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CALIFORNIA TUMOR TISSUE REGISTRY

SEVENTY-NINTH SEMI-ANNUAL SEMINAR

ON

TUMORS OF THE HEAD AND NECK

MODERATOR:

JOHN G. BATSAKIS, M. D.
CHAIRMAN, DEPARTMENT OF PATHOLOGY
THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER
M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE
HOUSTON, TEXAS

JAMES H. CREMIN, M. D.
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QUEEN OF ANGELS HOSPITAL
LOS ANGELES, CALIFORNIA

SUNDAY MAY 26, 1985
9:00 A.M. - 4:30 P.M.
REGISTRATION: 7:30 A. M.

SHERATON PLAZA LA REINA HOTEL
LOS ANGELES, CALIFORNIA

Please bring your protocol, but do not bring slides or microscopes to the meeting.

CONTRIBUTOR: Ronald W. Oxenhandler, M. D.
Chattanooga, Tennessee
John G. Batsakis, M. D.
Houston, Texas

MAY 1985 - CASE NO. 1

TISSUE FROM: Right submandibular gland

ACCESSION NO. 25405

CLINICAL ABSTRACT:

History: A 28 year old woman had bilateral submandilar gland enlargement.

Laboratory studies revealed a white count of 3200 with 40% lymphocytes and a total protein of 9.1 g. with albumin 3.9 g.

SURGERY:

The right submandibular gland was removed.

GROSS PATHOLOGY:

The gland was diffusely lobulated with a tan-yellow appearance.

CONTRIBUTOR: John G. Batsakis, M. D.
Houston, Texas

MAY 1985 - CASE NO. 2

TISSUE FROM: Palate

ACCESSION NO. 25404

CLINICAL ABSTRACT:

History: A 37 year old woman had a progressively enlarging mass at the junction of the hard and soft palate.

CONTRIBUTOR: Mark J. Beck, M. D.
Rancho Mirage, California

MAY 1985 - CASE NO. 3

TISSUE FROM: Left buccal and canine space

ACCESSION NO. 25087

CLINICAL ABSTRACT:

History: This man reported a 10 year history of a slowly growing mass in the left side of the oral cavity. The mass was interfering with mandibular function at the time of presentation.

Physical examination: A freely movable, non-tender mass was present.

SURGERY:

The mass was excised.

GROSS PATHOLOGY:

The specimen consisted of a 3.5 x 2.5 x 1.8 cm. tan brown glistening nodule.

CONTRIBUTOR: Kenneth Frankel, M. D.
Covina, California

MAY 1985 - CASE NO. 4

TISSUE FROM: Submandibular gland

ACCESSION NO. 24248

CLINICAL ABSTRACT:

History: A 76 year old woman noted nontender swelling in the region of the right submandibular gland for about 3 years.

SURGERY: (June 2, 1981)

The right submandibular gland was excised.

GROSS PATHOLOGY:

The gland measured 2.5 x 2.4 x 1.7 cm. and was almost completely replaced by an infiltrating, firm, pale gray mass.

CONTRIBUTOR: Luis Quan, M. D.
Anaheim, California

MAY 1985 - CASE NO. 5

TISSUE FROM: Right external auditory canal

ACCESSION NO. 25353

CLINICAL ABSTRACT:

History: This 7 year old white male presented with a firm, slowly enlarging mass in the right posterior external auditory meatus. This originally started as a small pimple and family recalcitrant to medical therapy and lancing of the ear.

SURGERY: (October 29, 1984)

An excision of the mass was performed.

GROSS PATHOLOGY:

A fragment of elongated polypoid tissue measuring 2.7 x 1.2 x 1.0 cm. was received, along with some smaller fragments aggregating to 0.6 cm. that were stated to be from the lesion's base.

CONTRIBUTOR: Sheldon L. Gee, M. D.
Lompoc, California

MAY 1985 - CASE NO. 6

TISSUE FROM: Left neck

ACCESSION NO. 25134

CLINICAL ABSTRACT:

History: This 50 year old man presented with an 11 cm., mobile, left neck mass in 1979. This was excised and a diagnosis of "lymphangioma" was given. In March and December 1981 two swellings were noted and thought to be recurrence at surgery. These were scar tissue. In November 1983, he presented with a recurrent left neck mass.

Physical examination: The left neck contained a 4 cm. in diameter, lobulated, mobile mass at the site of the previous surgical scar.

CT Scan: There was a well-circumscribed, 5.5 x 4 x 2 cm. mass just beneath the left sternocleidomastoid muscle.

SURGERY: (December 1983)

The left neck mass was excised.

GROSS PATHOLOGY:

The specimen was received as multiple, extremely soft pink-tan tissue nodules, some smooth and others convoluted. On section, some variations were noted with some nodules having pale, firm centers and others having softer, pink-tan centers.

CONTRIBUTOR: Sylvan Cohen, M. D.
Panorama City, California

MAY 1985 - CASE NO. 7

TISSUE FROM: Floor of mouth

ACCESSION NO. 24295

CLINICAL ABSTRACT:

History: A 67 year old male first noted a painless swelling of the floor of the mouth in 1976. There was gradual enlargment until July, 1978 when the mass was excised. The mass slowly recurred in the same location.

SURGERY: (May 18, 1981)

The mass was excised.

GROSS PATHOLOGY:

Multiple fragments of soft, tan tissue measuring 6 cm. in aggregate were received.

CONTRIBUTOR: Henry Tesluk, M. D.
Davis, California

MAY 1985 - CASE NO. 8

TISSUE FROM: Neck

ACCESSION NO. 24755

CLINICAL ABSTRACT:

History: A 74 year old woman first noted a tender mass in the front of the neck above the sternal notch about 10 months prior to admission. There was gradual enlargement of the mass with some respiratory impairment. The patient noted an 8 lb weight loss. There was no prior history of surgery.

Physical examination revealed some respiratory distress with excessive sweating and a symmetrical mass in the region of the trachea. The mass was large and nontender.

Radiograph: CT scan showed a well defined tumor mass extending between the posterior surface of the sternum and the aortic arch and extending laterally to both pleural reflection at the level of the sternum.

SURGERY: (November 29, 1982)

After an initial biopsy, the mass was excised. The tumor was intimately related to blood vessels in the base of the neck, extended behind the sternum to the carina, and was attached to the trachea.

GROSS PATHOLOGY:

The specimen was received in fragments and weighed 30 grams in aggregate. The pieces were firm and tan with an irregular, whorling cut surface. Some pieces showed infiltration into adjacent skeletal muscle.

CONTRIBUTOR: Sheldon Gee, M. D.
Lompoc, California

MAY 1985 - CASE NO. 9

TISSUE FROM: Maxillary sinus

ACCESSION NO. 25279

CLINICAL ABSTRACT:

History: A 64 year old male complained of swelling over the right cheek for two months. Two years previously, he began to notice loss of sensation in the distribution of the right infraorbital nerve. Eight years previously, a biopsy of a right cheek skin lesion revealed an "active junctional nevus" with atypical features. This skin lesion had recurred after a previous biopsy.

Physical examination revealed a doughy swelling over the right cheek. There was decreased sensation over the distribution of the right infraorbital nerve.

Radiograph: A CT Scan revealed a mass in the right maxillary sinus with destruction of sinus walls and the floor of the orbit.

SURGERY: (January 19, 1984)

A maxillectomy was performed.

GROSS PATHOLOGY:

The tumor measured 4.5 x 4 x 2 cm. and protruded from the maxillary sinus. The infraorbital nerve appeared to extend into a "loculation" of the tumor. Cut surfaces were white and firm.

CONTRIBUTOR: Raymond Bangle, M. D.
Tarzana, California

MAY 1985 - CASE NO. 10

TISSUE FROM: Nasal cavity

ACCESSION NO. 25110

CLINICAL ABSTRACT:

History: A two year old boy was found to have a large, bulky, polypoid tumor in the nasal cavity.

GROSS PATHOLOGY

The tumor measured 5 x 4 x 3.3 cm., and was covered by ulcerated respiratory mucosa.

CONTRIBUTOR: J. R. Phillips, M. D.
Fresno, California

MAY 1985 - CASE NO. 11

TISSUE FROM: Right buccal gingiva

ACCESSION NO. 24258

CLINICAL ABSTRACT:

History: A 67 year old woman noted a mass in the region of the right cheek for about 4 years.

Physical examination revealed a tumor located lateral to the posterior alveolar ridge on the right maxillary alveolus.

SURGERY: (March 5, 1981)

After a biopsy, the mass was resected.

GROSS PATHOLOGY:

The tumor measured 3 x 3 x 2.3 cm. and was covered on one surface by intact mucosa. Cut surfaces revealed sharply circumscribed, gray, whorled tissue with focal hemorrhage.

CONTRIBUTOR: Sheldon A. Miller, M. D.
Camarillo, California
Joseph M. Mirra, M. D.
Los Angeles, California

MAY 1985 - CASE NO. 12

TISSUE FROM: Left maxillary sinus

ACCESSION NO. 25310

CLINICAL ABSTRACT:

History: The patient complained of left sided headaches and left sided epistaxis. She saw a physician who referred her to UCLA where it was noted that the nasal obstruction had been present 9 months before admission. The patient stated she thought it was an allergy.

Physical examination: The left upper nasal cavity was filled with friable roughened surface tumor, unclear origin. On the right side there was no tumor although the septum was pushed laterally posteriorly.

SURGERY:

Extended left medial maxillectomy with sphenoidomy, resection of medial orbital wall and septectomy were performed.

GROSS PATHOLOGY:

The specimen consisted of 4 fragments of tumor and bone which ranged from 1.7 x 0.9 x 0.4 cm. to 5.5 x 3.5 x 3.5 cm. and weighed in total 45 grams. The tumor was hard, white gray and had a nodular translucent appearance. In some areas it was easily separated from the surrounding soft tissues and bone and in other areas it was firmly attached and appeared to infiltrate through the bone.

CONTRIBUTOR: John Gmelich, M. D.
Pasadena, California

MAY 1985 - CASE NO. 13

TISSUE FROM: Mandible

ACCESSION NO. 24434

CLINICAL ABSTRACT:

History: A 65 year old male complained of numbness of his lower lip and swelling along the right jaw for two months. An x-ray revealed a tumor in the right mandible.

SURGERY: (November 30, 1981)

After an initial biopsy, a segmented resection of the mandible was performed.

GROSS PATHOLOGY:

The mandible contained an area of "swelling" measuring up to 1.5 cm. in diameter.

CONTRIBUTOR: Carl P. Treling, M. D.
Los Angeles, California

MAY 1985 - CASE NO. 14

TISSUE FROM: Left internal jugular vein and surrounding tissues

ACCESSION NO. 25190

CLINICAL ABSTRACT:

History: This 60 year old woman had a 1 year history of pulsating tinnitus involving the left ear.

Physical examination: On otoscopic examination, a pink mass was vaguely discernible behind the left tympanic membrane. It was non-pulsatile.

CT Scan: An enchancing mass lesion involving the left parapharyngeal space and jugular fossa was present.

SURGERY: (January 1983)

At surgery, the tumor itself was found to lie within the lumen of the internal jugular vein, and had infiltrated through the wall of the vein, and into the surrounding soft tissues. A resection of the mass was performed.

GROSS PATHOLOGY:

The main portion of the specimen consisted of a 8.5 x 1.2-1.5 cm. portion of jugular vein. Upon opening the vessel, it was observed to contain a 3.0 x 1.5 cm., smooth, cylindrical grey-tan soft, rubbery mass attached firmly to the wall. Section of the mass revealed a slightly bulging pink-tan interior. The vein wall was thickened at the point of tumor attachment, and tumor was identified extending through the adventitial surface of the wall. Several portions of red-tan soft tissue from the area surrounding the vein were also submitted. The largest of those measured 0.8 x 0.4 x 0.3 cm.

CONTRIBUTOR: Carl P. Treling, M. D.
Los Angeles, California

MAY 1985 - CASE NO. 15

TISSUE FROM: Nose

ACCESSION NO. 25189

CLINICAL ABSTRACT:

History: This 44 year old Honduran man presented with a large mass in the left nasal cavity with extension into the left orbit. He gave a history of epistaxis from the left nostril, left proptosis and left-sided headache for 3 years prior to his presentation.

Physical examination: The patient had a marked left proptosis with lateral deviation of the affected eye. Bulging of the left lateral nasal area was noted, along with a mucous coated mass in the left superior nasal cavity. An incomplete left central facial palsy was present.

CT Scan: A mass lesion involving all of the sinuses on the left side, with nasal and intracranial involvement was identified.

SURGERY: (April 1983)

A lateral rhinotomy with exenteration of the superior left maxilla, ethmoid, sphenoid and septum was performed.

GROSS PATHOLOGY:

The specimen consisted of multiple portions of bone and tumor. The largest single tumor mass measured 6.0 x 2.0 x 1.5 cm., was red-tan and had a rubbery consistency.

CONTRIBUTOR: Robert Failing, M. D.
Santa Barbara, California

MAY 1985 - CASE NO. 16

TISSUE FROM: Tongue

ACCESSION NO. 25348

CLINICAL ABSTRACT:

History: A 75 year old male with a long history of cigarette smoking and alcoholism complained of a gradually enlarging, tender ulcer on the right side of the tongue. Biopsy performed and admitted for surgical treatment.

Physical examination revealed an ulceration, indurated lesion of the right mid-posterior tongue, and also adenopathy in the right submandibular and sternocleidomastoid areas.

SURGERY: (November 1, 1984)

At surgery, in the right upper internal jugular chain there was a 2 cm. hard firm lymph node in the posterior third of the tongue, just anterior but involving slightly circumvid papilla was a large 2 x 1.5 cm. ulcerating lesion of the tongue which was very mobile. A right hemiglossectomy and radical neck dissection were performed.

GROSS PATHOLOGY:

A 4.0 x 2.5 x 1.2 cm. firm, pale, tan, ulcerated tumor was present on the dorsal surface of the tongue. Four cervical lymph nodes were involved by metastatic tumor.

CONTRIBUTOR: W. K. Bullock, M. D.
Los Angeles, California

MAY 1985 - CASE NO. 17

TISSUE FROM: Nasal cavity

ACCESSION NO. 24824

CLINICAL ABSTRACT:

History: This 71 year old man had a 3 month history of left nasal obstruction and left nostril epistaxsis. The past medical history was remarkable for lymphosarcoma, lymphocytic type, in cervical lymph nodes 9 years previously. This was treated with chemotherapy.

Physical examination: There was a large, bleeding nasal mass obstructing the left nasal passage.

SURGERY: (February 1983)

Removal of the nasal mass was performed.

GROSS PATHOLOGY:

The specimen consisted of multiple fragments of gray to tan tissue fragments which measured up to 1.5 x 1.0 x 1.0 cm. These aggregated to 3 grams. Also present was a pale grey, hemorrhagic polypoid structure which measured 2.8 x 2.0 x 1.0 cm.

CONTRIBUTOR: Weldon K. Bullock, M. D.
Los Angeles, California

MAY 1985 - CASE NO. 18

TISSUE FROM: Left ethmoid vault

ACCESSION NO. 24954

CLINICAL ABSTRACT:

History: This 59 year old woman presented with a complaint of difficulty breathing through the left nostril.

Physical examination: A "huge" mass was present in the left ethmoid vault, anterior and medial to the middle turbinate.

SURGERY: (June 1983)

The mass was removed.

GROSS PATHOLOGY:

The specimen consisted of 18 grams of nodular, blood-covered tissue and one light tan, polypoid mass which measured 3.0 x 1.0 x 1.0 cm. On section, this mass was cystic and contained white, mucoid material. The blood-covered masses ranged in size from 2.0 x 1.0 x 1.0 cm. to 2.5 x 1.5 x 1.5 cm. Many of those had cystic interiors on section, with cysts up to 1.0 cm. in dimension. The cut surfaces varied in color from mottled white to red to yellow.

CONTRIBUTOR: H. V. O'Connell, M. D.
Bakersfield, California

MAY 1985 - CASE NO. 19

TISSUE FROM: Nose

ACCESSION NO. 24885

CLINICAL ABSTRACT:

History: This 40 year old man had a long standing history of right nasal polyps. He presented with a chief complaint of enlargement and bleeding of these polyps.

SURGERY: (February 1983)

A nasal polypectomy was performed.

GROSS PATHOLOGY:

The specimen consisted of multiple irregularly-shaped pieces of soft tissue, some of which had a glistening, polypoid appearance. It aggregated to 16 grams.

CONTRIBUTOR: E. G. Edwards, M. D.
Santa Ana, California

MAY 1985 - CASE NO. 20

TISSUE FROM: Right maxilla

ACCESSION NO. 22551

CLINICAL ABSTRACT:

History: A 25 year old Mexican male was found to have a mass in the right maxilla bulging into the nasal cavity.

Physical examination: A mass was found in the right maxilla bulging into the nose.

SURGERY: (July 28, 1977)

A right maxillectomy was performed.

GROSS PATHOLOGY:

The tumor measured 5 x 5 x 3.5 cm. and filled and distended the maxillary antrum. The tumor also extended downward between the maxillary teeth. The mass was multicystic, the cyst walls containing bone, and the cysts containing blood.

CONTRIBUTOR: Harry Pappas, M. D.
Lancaster, California

MAY 1985 - CASE NO. 21

TISSUE FROM: Floor of mouth

ACCESSION NO. 24987

CLINICAL ABSTRACT:

History: An 85 year old woman complained of pain in the floor of the mouth for several months.

Physical examination revealed a tumor within the soft tissues of the floor of the mouth.

Radiograph: X-rays disclosed a heavily calcified mass in the region of the sublingual gland.

surgery; (July 26, 1983)

The mass which was unattached to bone and appeared to be confined to the genioglossus muscle was excised.

GROSS PATHOLOGY:

The tumor measured 4 x 3 x 1.5 cm. and was firm. Cut surfaces revealed solid, gray-white tissue.

CONTRIBUTOR: Marcus Contardo, M. D.
Oceanside, California

MAY 1985 - CASE NO. 22

TISSUE FROM: Larynx

ACCESSION NO. 24453

CLINICAL ABSTRACT:

History: This 59 year old man presented with symptoms of laryngeal obstruction.

Past medical history was remarkable for a prior diagnosis of "chondroma" made on laryngeal biopsy.

Physical examination: Laryngoscopy revealed a large, rubbery, seemingly encapsulated mass obstructing the larynx.

SURGERY:

The patient underwent a total laryngectomy.

GROSS PATHOLOGY:

The right larynx was occupied by a large, nodular, rubbery mass with a translucent grey cut surface and multiple small foci of calcification. The tumor appeared to be completely confined to the larynx. It measured 4 x 4 x 2.5 cm. in greatest dimension.

CONTRIBUTOR: Margarete Rose, M. D.
Culver City, California

MAY 1985 - CASE NO. 23

TISSUE FROM: Vocal cord

ACCESSION NO. 25266

CLINICAL ABSTRACT:

History: An 83 year old Oriental male developed persistent hoarseness 5 months prior to admission. At laryngoscopy, a mass was found arising from the anterior portion of the left vocal cord. Four years previously the patient was found to have colon cancer, and a right colectomy was performed.

SURGERY: (June 11, 1984)

The tumor was excised.

GROSS PATHOLOGY:

The mass measured 1.3 x 1.0 x 0.7 cm., was pink tan and smooth. The cut surface was amber, moist and glistening.

CONTRIBUTOR: Richard H. Kelty, M. D.
Thousand Oaks, California

MAY 1985 - CASE NO. 24

TISSUE FROM: Submandibular gland

ACCESSION NO. 25330

CLINICAL ABSTRACT:

History: This 89 year old woman presented with a painless right cervical mass that had been present for several months.

Past medical history was significant for a Clark's level III malignant melanoma excised from her right cheek 4 years previously.

SURGERY: (August 27, 1984)

The mass was excised.

GROSS PATHOLOGY:

The specimen consisted of a lobulated, grey-tan tissue mass measuring 2.5 x 2.5 x 1.5 cm. On section, parts of it's interior appeared to be necrotic.

CONTRIBUTOR: D. R. Dickson, M. D.
Santa Barbara, California

MAY 1985 - CASE NO. 25

TISSUE FROM: Mandible

ACCESSION NO. 23031

CLINICAL ABSTRACT:

History: This 74 year old man had a hemimandibulectomy and right neck dissection for a diagnosis of oral cavity squamous cell carcinoma. He was treated with 6400 rads of radiation prior to the surgical procedure. Four years later he presented with recurrent tumor of the right jaw and oral cavity with multiple cutaneous fistulae.

SURGERY: (January 27, 1978)

A wide excision of the remaining right jaw and oral cavity with partial glossectomy and suprahyoid dissection was performed.

GROSS PATHOLOGY:

The specimen weight 140 gram, measured 108 mm. in greatest dimension and contained skin, subcutaneous tissue, a portion of mandible buccal mucosa and a portion of tongue and pharyngeal wall. The buccal mucosa showed extensive ulceration and multiple fistulous tracts, which were lined with granular pink to dull yellow-red material. Sectioned surfaces revealed a hard, irregular, yellow-white mass infiltrated the submucosal and subcutaneous tissues.

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TUMORS OF THE HEAD AND NECK

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MAY 26, 1985

DIAGNOSTIC INDEX

DIAGNOSITC INDEX (CONT.)

Case 1. Lymphoepithelial lesion; submandibular gland

Without clinical or laboratory supporting evidence, surgical pathologists are not entitled to make a diagnosis of Sjogren's syndrome even though the salivary lesional tissue – the lymphoepithelial lesion is the universal finding in the syndrome.

The seminar case is fairly characteristic of the lymphoepithelial lesion with epimyoepithelial islands and replacement of the acinar parenchyma by lymphoid cells. In some foci the lymphoid cells, particularly about the islands exhibit atypism. While insufficient for diagnosis, at this stage, it is of interest that the patient developed an extra-nodal immunoblastic sarcoma in the residual submandibular and sublingual glands, one year later. The accompanying reprints details the clinicopathologic aspects of this fascinating lesion.

THE PATHOLOGY OF HEAD AND NECK TUMORS: THE LYMPHOEPITHELIAL LESION AND SJÖGREN'S SYNDROME, PART 16

JOHN G. BATSAKIS, MD

Abstract: The clinical disorder Sjögren's syndrome and its putative histologic marker in salivary tissues, the lymphoepithelial lesion, have been and continue to be sources of confusion as well as the subjects of extensive immunologic and pathologic research. At the present time, Sjögren's syndrome is defined as a lymphocyte-mediated exocrinopathy but definition does little justice to the profound immunogenetic basis of the syndrome. This report presents a contemporary review of the lymphoepithelial lesion and the syndrome and presents a hypothesis of pathogenesis based on a graft vs host disease-like disorder. The hypothesis incorporates the immunogenetic, immunoregulatory, and neoplastic aspects of Sjögren's syndrome.

HEAD & NECK SURGERY 5:150–163 1982

Nonneoplastic diseases of the salivary glands continue to be sources of frustration for head and neck surgeons and surgical pathologists. Unassisted by our inchoate knowledge of pathologic processes the management of patients with these diseases is often empirical, and the results are often disappointing. One disease stands out. In its histopathologic expression in salivary glands it is called lymphoepithelial lesion. In its various clinical presentations it has been called Mikulicz's disease or syndrome, sicca syndrome, and Sjögren's disease or syndrome.[1]

The intensity of research in the disease places it in the forefront of investigations of diseases of altered immunoregulation. This review is intended to serve two purposes: (*1*) to present the clinicopathologic features of the disease and (*2*) to summarize the current progress in understanding the pathogenesis of the disease.

LYMPHOEPITHELIAL LESION

The term "lymphoepithelial lesion" of salivary tissues is descriptive and while some authors[2,3] use it synonymously with "immune sialadenitis," it should remain a histopathologic designation without specific pathogenic implications or translation into a broader clinical context. It is a pathologic process primarily of the parotid glands that is found in two different clinical conditions. One is a local salivary gland disease that affects both male and female patients and the other is a systemic disorder (Sjögren's syndrome) that almost always (95%) affects women.

The lymphoepithelial lesion is characterized by three basic microscopic findings: (*1*) hyperplastic metaplasia of ductal epithelium, (*2*) lym-

Figure 1. Lymphoepithelial lesion of parotid gland removed from a patient with primary Sjögren's syndrome. The only residual parenchymal elements remaining are epimyoepithelial islands. Hematoxylin and eosin, ×140.

Figure 2. Epimyoepithelial island surrounded by lymphoid cells that have replaced the functional parenchyma of the parotid gland. Hematoxylin and eosin, ×180.

phoid cell infiltration of the functional parenchyma and (3) atrophy of acini. Each of these becomes progressively more severe until, in the unremitted disease, the involved salivary gland becomes totally effaced by lymphoid cells, leaving only islands of residual deformed ducts (Fig. 1).

From a purely histopathologic viewpoint the salivary gland process originates in and about intralobular ducts, which first appears as a chronic punctate parotitis.[4,5] The ducts are dilated, their cells disrupted and flattened, and an epidermoid metaplasia begins. Chronic inflammatory cells aggregate around the ducts. These cells are predominantly lymphocytes. The acinar atrophy appears to be secondary to the duct changes. The duct perturbations continue as the lymphoid cells progressively increase in number and become confluent. With time, the ductal lumens are obliterated by the metaplasia and hyperplasia of the lining cells and eventuate into epimyoepithelial islands. Embryologically the transformation of salivary tissue enclaved in parotid lymph nodes follows a similar pattern.

Depending on the stage of the disease the lymphoid infiltrate will contain variable numbers of plasma cells and macrophages. The interstitium may show irregular collagenization and, in rare instances, amyloid. Some lesions have excess basement membrane material around the epimyoepithelial islands (Fig. 2).

Although the islands in the lesions are called epimyoepithelial, definite proof of myoepithelial cell participation is elusive; this is testimony, once again, to the difficulty in identifying these cells in a state other than their normal one.[6,7]

SJÖGREN'S SYNDROME

What began as a nosological misadventure with Mikulicz's description of the clinical and pathologic findings in a single patient has evolved into a complex disorder or group of disorders that has been the subject of intensive immunogenetic studies. It has become clear that a clinical or pathologic diagnosis of Mikulicz's disease or syndrome is so ambiguous and so ill-defined that it should never be used. As so often happens, however, one eponymic designation is succeeded by another, implying a better understanding of the

disease process. So now Sjögren has replaced Mikulicz.

On the basis of current evidence, Sjögren's syndrome is the result of lymphocyte-mediated destruction of exocrine glands, which in turn leads to diminished or absent glandular secretions and mucosal dryness.[8] Classified as an autoimmune disorder, Sjögren's syndrome is now regarded as the second most common rheumatic disorder, exceeded in incidence only by rheumatoid arthritis.[8,9]

The clinical diagnosis of Sjögren's syndrome is considered to be made when there is objective evidence for two out of three major criteria: (*1*) xerophthalmia (presence of keratoconjunctivitis sicca), (*2*) xerostomia, and (*3*) an associated autoimmune rheumatic disorder.[8,9] In some clinics an abnormal minor salivary gland biopsy (usually labial) showing lymphocytic infiltration has replaced the clinical finding of xerostomia.[9]

The sicca complex obviously holds a central place in the clinical diagnosis. Ocular symptoms are, however, nonspecific and may be so subtle that they are missed. Nonspecificity applies also to the xerostomia.

Primary and Secondary Sjögren's Syndrome. Sjögren's syndrome may be clinically divided into two types, a primary or limited form and a secondary or complete form.[8] In the secondary form, the diagnostic triad is complete in that there is an accompanying autoimmune disease.[8,9] This is most often rheumatoid arthritis (48% out of 313 cases of Sjögren's syndrome reviewed by Snider).[10] Systemic lupus erythematosus, scleroderma, and polymyositis follow distantly, and other autoimmune diseases associated with Sjögren's syndrome include: mixed connective tissue disease, primary biliary cirrhosis, chronic active hepatitis, thyroiditis, vasculitis, chronic graft-vs-host disease, mixed cryoglobulinemia, and hypergammaglobulinemic purpura. Polyarteritis is rarely reported with Sjögren's syndrome.

Primary Sjögren's syndrome, or the limited form, is commonly referred to as the sicca syndrome, but in view of its often systemic nature it should be more descriptively called the sicca systemic syndrome. The sicca components are but parts of a variable systemic disease. In the full expression of the sicca systemic syndrome, ocular and oral signs and symptoms predominate, but true to its diffuse exocrinopathic involvement several or all exocrine gland systems may be involved. An intermittent unilateral or bilateral parotid or other salivary gland enlargement occurs in 80% of the patients. Lacrimal gland swelling is not common. Other exocrine gland targets include the upper and lower respiratory tracts, the gastrointestinal tract, skin, and vagina.[8-10] Dry and sometimes scaly skin is often seen, and in patients with severe disease biopsy specimens have shown lymphoid cell infiltrates in sweat glands.[8] The vulva may be similarly involved. Dryness of the vagina is accompanied by dyspareunia. Dryness and crusting of the nose with epistaxis and even septal perforation may occur. There may be sinusitis. Otitis media follows obstruction of the Eustachian tubes and laryngeal involvement can give rise to hoarseness. A usually dry cough occurs in about a quarter of patients.[10] Atelectasis, recurrent pneumonia and, at times, pleural effusions are complications of the involvement of pulmonary mucoserous glands. Pulmonary findings are more often seen in patients with the primary syndrome. Biopsy specimens manifest lymphoid infiltrates in the glands of the nasal cavity, pharynx, larynx, trachea, and bronchi.[8-10]

In the primary form of the syndrome extraglandular findings are not uncommon and are pathogenetically important. Extraglandular, in this context, refers to the spread of the lymphoproliferative process in exocrine tissues to the reticuloendothelial system, kidneys, muscle, and lungs.[8,10,11] The most common renal lesion is an interstitial lymphocytic infiltrate with tubular atrophy and fibrosis (Fig. 3). This is either not apparent clinically or is manifested as hyposthenuria, a renal tubular acidification defect (with or without acidemia), nephrogenic diabetes insipidus, Fanconi's syndrome, or infrequently as compromised renal function.[8] An indolent myositis is the presentation when there is muscle involvement. A demonstrable vasculitis occurs in less than 10% of patients with primary Sjögren's syndrome, but patients with extraglandular spread have a higher incidence of Raynaud's phenomenon and intermittent dependent purpura than patients with the restricted glandular type of the disease.[10] The lungs may be the sites of an intense lymphocytic infiltration, radiographically presenting as multiple infiltrates, fibrosis, or diffuse interstitial pneumonitis. The thyroid gland may exhibit a lymphocytic thyroiditis (Fig. 4).

Immunology. The immunologic aberrations in patients with Sjögren's syndrome are even more complex than the clinicopathologic presenta-

Figure 3. Specimen from a kidney of a patient who died with primary Sjögren's syndrome and extraglandular lymphoid cell infiltrates. Glomeruli are not affected. Note the interstitial nephritis. Hematoxylin and eosin, ×200.

Figure 4. Thyroid gland tissue from patient described in Fig. 3. Note the lymphoid infiltrate where epidermoid islands occur. Hematoxylin and eosin, ×200.

tions.[8-11] The prevailing abnormality appears to be a hyperreactivity at the B (bursa-derived) lymphocyte level, which is polyclonal.[8,11]

Hyperreactivity of B-cell function may be a primary phenomenon or may be directly or indirectly related to alterations in such immunoregulatory mononuclear cells as thymus-derived (T) cell subpopulations.[12,13] Polyclonal activation of B cells in Sjögren's syndrome may reflect one or more underlying processes. Activation of multiple B-cell clones may originate as a nonspecific trigger by a true polyclonal activator. Alternatively, the original stimulus may be specific but may lead to a secondary polyclonal activation of either multiple B-cell or T-cell clones, or both. Modulation of the B-cell response by immunoregulatory T cells is clearly implied but not yet defined. Monocyte-macrophages can also modulate the response either directly on the B cells or through accessory T-cell subpopulations.

There is abundant laboratory evidence of B-cell hyperreaction in Sjögren's syndrome. Findings include polyclonal hypergammaglobulinemia, non-organ-specific autoantibodies, and antibodies to extractable nuclear antigens.[8,9]

Four separate autoantibodies have been found in sera from patients with Sjögren's syndrome (Table 1).[8] One is the organ-specific antisalivary duct antibody and the other three are nonorgan specific. Although salivary duct antibodies are of pathogenic importance, they are of little help in diagnosis. Their concentration varies inversely with the degree of lymphoid infiltrate in salivary tissues, and an increase is found in only one fourth of patients with primary Sjögren's syndrome.[8] Table 2 presents autoantibody and other clinical laboratory findings in Sjögren's syndrome. The percentages given are maximum expressions.[11]

Lip Biopsy and Sjögren's Syndrome. Since it is a lymphocyte-mediated exocrinopathy, Sjögren's syndrome manifests histopathologic alterations in the minor as well as major salivary tissues.

Table 1. Autoantibodies in Sjögren's syndrome.*

Antibody	Occurrence
I. Organ specific antisalivary duct antibody	
II. Nonorgan specific	
SS-A	Found in patients with primary Sjögren's syndrome but not in the syndrome with rheumatoid arthritis.
SS-B (Ha)	Found in patients with Sjögren's syndrome alone or in association with systemic lupus erythematosus.
SS-C (RAP, RANA)	Found in patients with rheumatoid arthritis with or without Sjögren's syndrome but not in patients with primary Sjögren's syndrome.

*Prepared from data presented by Moutsopoulos and co-workers.[8] SS Sjögren's syndrome; Ha, after the patient in whom the antibody was first discovered; RAP, rheumatoid arthritis precipitin; RANA, rheumatoid arthritis associated nuclear antigen.

This has led to widespread use of the biopsy of several minor salivary gland sites to help establish the diagnosis and to monitor the progression of the disease. Salivary glands in the mucosa of the lower lip, palate, and nasal septum all have been biopsied, but labial biopsy is the most popular.[14-18]

That labial mucous glands are among the targets of immune disorders other than Sjögren's syndrome is clear from the results of biopsy in patients with rheumatoid arthritis, scleroderma, lupus erythematosus, sarcoidosis, amyloidosis, and graft-vs-host disease.[14,19] A relatively high percentage (58%) of positive lip biopsies has been reported by Nessan and Jacoway[20] in patients with sarcoidosis (Figs. 5 and 6). Although lip biopsy specimens have been reported to have shown that some collagen diseases have undergone distinctive changes, differential diagnosis is probably not achievable. Increased collagen deposition in the intralobular and extralobular connective tissue is typical for scleroderma (Fig. 7), but some cases of systemic lupus erythematosus, rheumatoid arthritis, sicca syndrome, and chronic graft-vs-host disease also show the same changes.

Clinical interpretations of the histologic findings in a labial biopsy require they be made within the context of the suspected disease. Also, not all patients with Sjögren's syndrome have positive lip biopsies.

The histologic changes in the lip's salivary tissue in a patient with Sjögren's syndrome are those seen in the major salivary glands, that is, a lymphocytic and plasma cell infiltrate of lobules with replacement of functional acinar parenchyma, accompanied by dilation of ducts and duct cell metaplasia (Fig. 8). Epimyoepithelial islands are seen only rarely in lip biopsy specimens but more often in palate biopsies.

Most control subjects do not manifest lymphocytic infiltration of labial mucous glands, but if they do, the quantity of cells is low and would not merit a histologic diagnosis of focal lymphocytic adenitis.[18] Thus, a somewhat objective scoring system of the degree of glandular involvement has been devised (Table 3).[15,16] An absence of lymphocytes is a grade 0. A grade 3 or 4 biopsy specimen strongly correlates with Sjögren's syndrome (Fig. 9). A focus is defined as an aggregate of 50 or

Table 2. Clinical laboratory findings in Sjögren's syndrome.*

Laboratory observation or finding	% of patients with abnormality
Anemia	80
Leukopenia	50
Increased erythrocyte sedimentation rate	90
Hypergammaglobulinemia	90
Rheumatoid factor	75
Cryoglobulinemia	20
Decreased complement	35
Circulating immune complexes	80
Antinuclear antibody	90
Antisalivary duct antibody	25
Antibodies to gamma globulin	80
Antibodies to native DNA	0
Antibodies to extractable nuclear antigens	
SS-A	80
SS-B	70
RANA (Rheumatoid arthritis-associated nuclear antigens)	30
RAP (Rheumatoid arthritis precipitin)	15

*Modified from Batsakis and Howard.[11] See Table 1 for abbreviations.

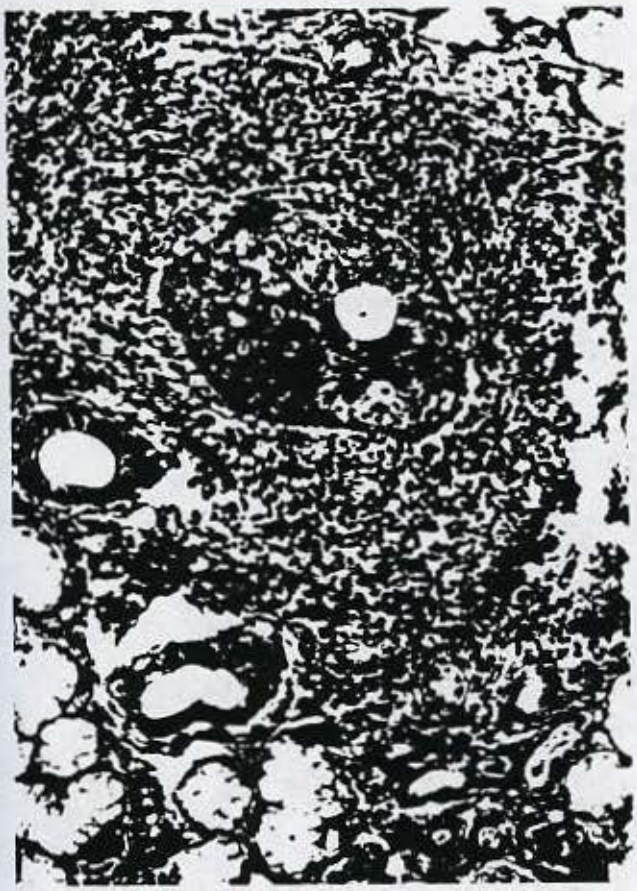

Figure 5. Lip biopsy specimen from a patient with sarcoidosis. Note the epimyoepithelial island set in a lymphoid cell aggregate. Hematoxylin and eosin, ×120.

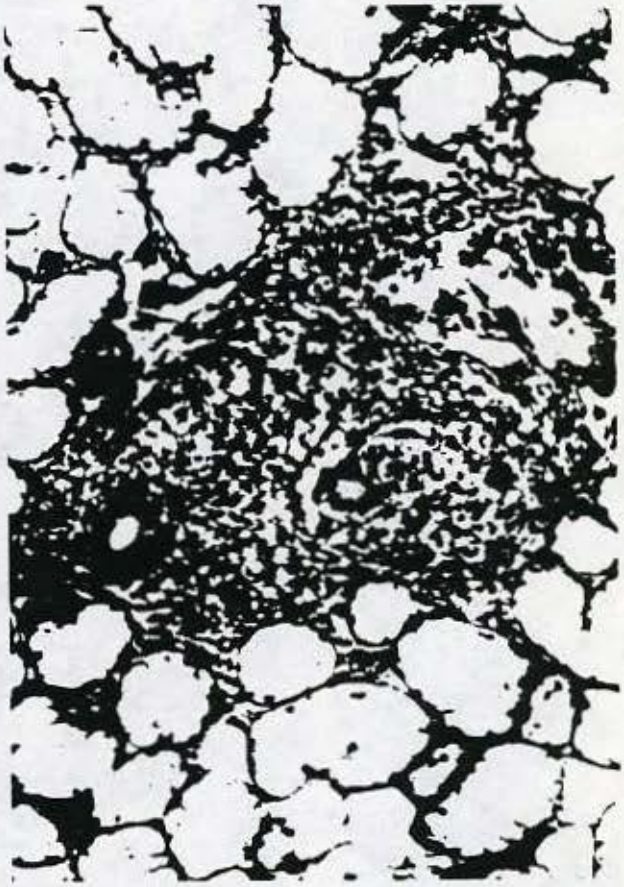

Figure 6. Lip biopsy specimen from patient described in Figure 5. Sarcoidal granuloma in mucous glands. Hematoxylin and eosin, ×200.

more lymphocytes, histiocytes, or plasma cells and is equivalent to focal adenitis of salivary tissues (Figs. 10 and 11). Tarpley and associates[16] have pointed out that patients with high-score grades or dense infiltrates also have fewer total lobules replaced by the infiltrates. This suggests that antigenicity may be localized in ductal and lobular areas within the gland rather than involve the entire gland in a uniform manner.

MALIGNANCY AND THE LYMPHOEPITHELIAL LESION AND SJÖGREN'S SYNDROME

Either the lymphoid or the epimyoepithelial components of the lymphoepithelial lesion can give rise to malignancy;[21] however, the event is

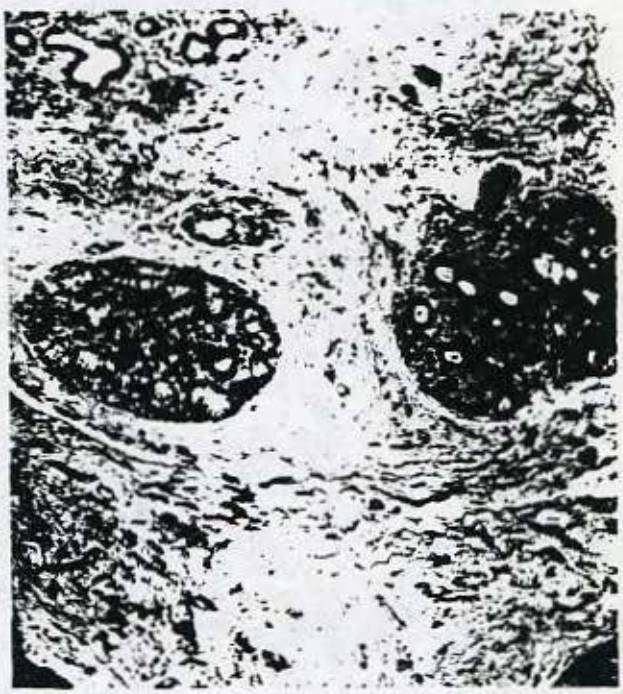

Figure 7. Lip biopsy specimen from a patient with scleroderma. Although the histopathologic changes in this patient differ sharply from that in Sjögren's syndrome, other patients with scleroderma have alterations more like that observed in the syndrome. Hematoxylin and eosin, ×80.

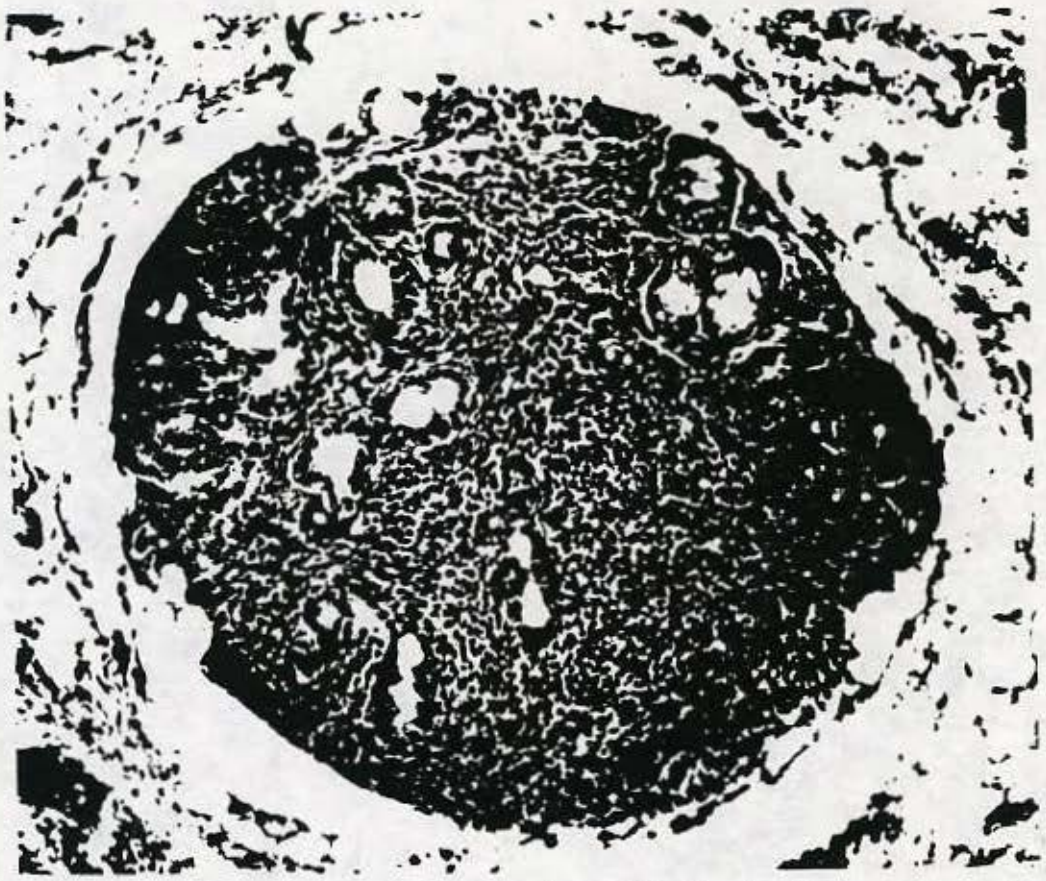

Figure 8. Sjögren's syndrome. This labial salivary gland lobule is almost completely replaced by lymphoid cells. Few acini remain. Hematoxylin and eosin, ×200.

uncommon, even rare. The intensity of immunologic research in Sjögren's syndrome and the increased risk of developing a lymphoma manifested by patients with the syndrome have obscured the fact that the lymphomas are almost always extrasalivary (Figs. 12 and 13). Indeed, it is difficult to document a transition from a preexisting benign lymphoepithelial lesion of the salivary gland to an intrasalivary lymphoma.[21,22] Carcinomas arising in a lymphoepithelial lesion also require histologic evidence of a prior benign tumor.

Table 3. Histologic grading of labial salivary tissue biopsies.*

Grade	Histologic definition
1	Slight lymphocytic infiltrate
2	Moderate infiltrate or less than one focus/4 sq mm
3	One focus per 4 sq mm
4	More than one focus per 4 sq mm

*From data presented by Greenspan and co-workers[15] and Tarpley and co-workers.[16]

Lymphomas and Lymphoepithelial Lesions. Malignant lymphomas develop in up to 5% of patients with Sjögren's syndrome. On the basis of a National Institutes of Health study of 136 women with the syndrome, the risk of lymphoma is about 6.4 cases per 100 cases of Sjögren's syndrome per year.[8] The relative risk in this group of patients was calculated to be approximately 44 times that expected in the normal population.[8]

The lymphomas have all been non-Hodgkin's type and they have been almost exclusively extrasalivary; nodal, extranodal, or combined. Waldenstrom's macroglobulinemia does occur, but less often.

Nearly all authors have commented on the difficulty in classifying the lymphoma that occurs in patients with Sjögren's syndrome.[9,23-25] In part, this relates to the evolution of classification schemes for the lymphomas, and, in part, to a lack of definition of the pseudolymphoma state that is believed to be an intermediate stage between polyclonal lymphoproliferation and lymphoma.[21,23] From my experience, the lymphomas are not nodular (diffuse), they have a large cell

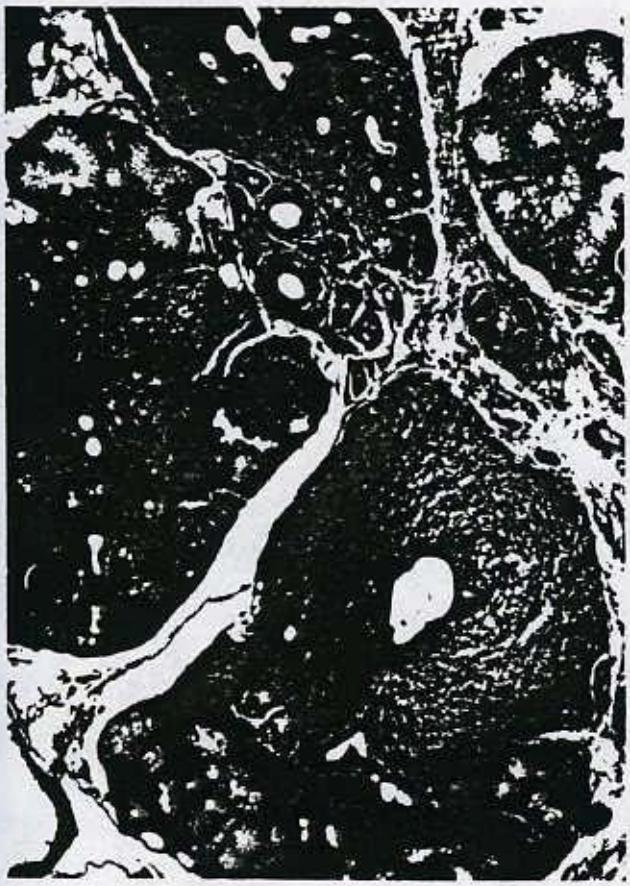

Figure 9. Low-magnification view of the labial biopsy shown also in Figure 8. All lobules are involved in a high-grade (3–4) score. Hematoxylin and eosin, ×60.

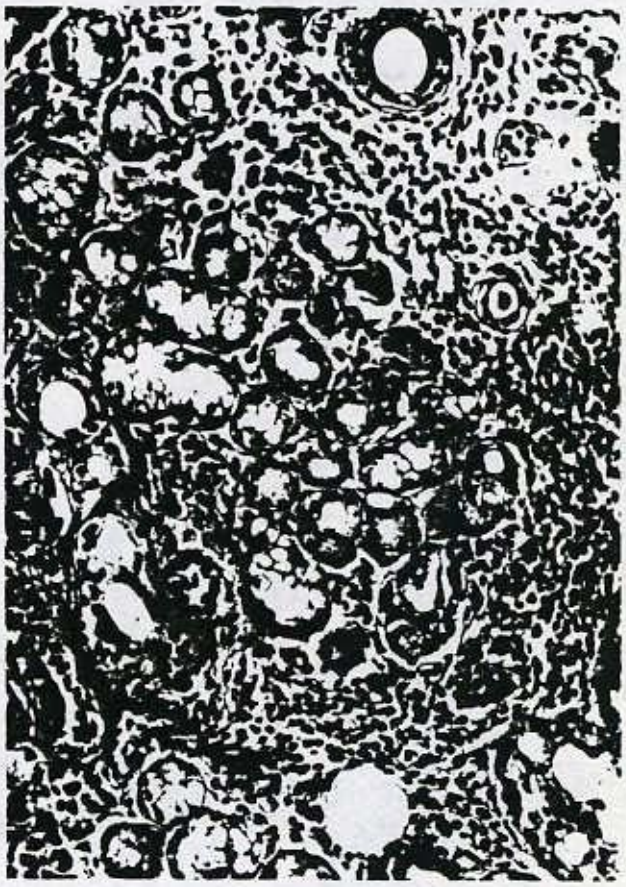

Figure 10. Low-score labial biopsy specimen from a patient with Sjögren's syndrome. Hematoxylin and eosin, ×200.

cytomorphology, and they conform to present day criteria for immunoblastic sarcoma or poorly differentiated diffuse lymphocytic lymphoma. Immunologic typing of the lymphomas indicates they are monoclonal (almost all IgM kappa) B-cell neoplasms.[26] Whether the Sjögren's-associated lymphomas are more biologically aggressive than conventional lymphomas has not been established.

Carcinoma ex Lymphoepithelial Lesion. This malignancy arises from the epithelial component of the lymphoepithelial lesion and is not related to Sjögren's syndrome. Because "malignant lymphoepithelial lesion" is an imprecise diagnostic term usually referring to lymphoma, I use "carcinoma ex lymphoepithelial lesion" for this rare salivary gland carcinoma.

Before accepting the diagnosis it is mandatory that a metastatic nonkeratinizing squamous cell carcinoma to parotid lymph nodes from the nasopharynx and Waldeyer's ring epithelium be excluded. More caution than usual is necessary since the two carcinomas can be remarkably similar in their histologic expression.

Currently there have been only 27 cases reported.[27] Almost all patients have been male and the primary site has been the parotid gland, except for one site in the submandibular gland. The tumor has always been unilateral and there have been no systemic manifestations of an associated disease, that is, Sjögren's syndrome.

Most of the carcinomas have been in Eskimos (15 of 27 cases) but this racial implication may only be a distortion in reporting these cases.

Low-power microscopic evaluations of the carcinomas give the impression of grotesque caricatures of the islands found in benign lymphoepithelial lesions set in a lymphoid stroma (Fig. 14). The neoplastic islands are composed of nonkeratinizing epidermoid cells and often exhibit coagulative necrosis; this is never seen in the benign precursor lesions. Electron-optic study has demonstrated the cells to be of a squamous lineage.[27]

Metastases occur to the cervical and retro-

Figure 11. High-score labial biopsy specimen from a patient with Sjögren's syndrome. Hematoxylin and eosin, ×200.

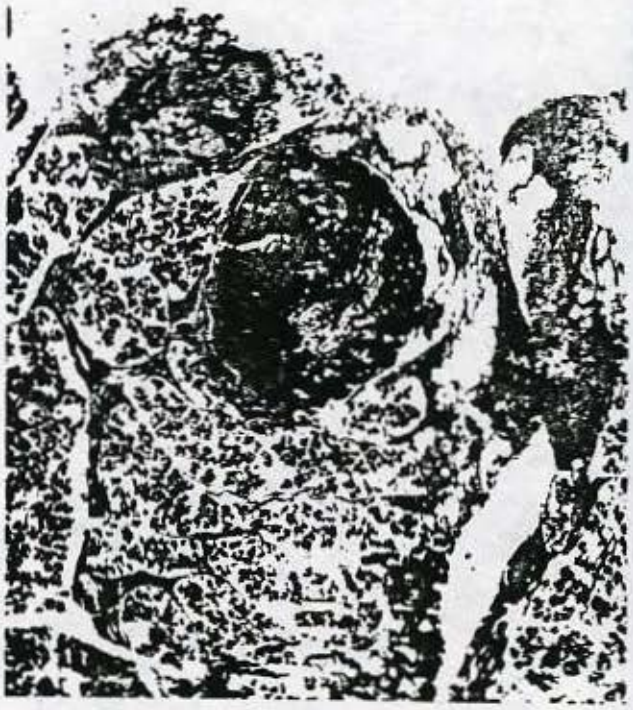

Figure 12. Poorly differentiated lymphocytic lymphoma of intraparotid lymph nodes. The patient did not have Sjögren's syndrome or a preexisting lymphoepithelial lesion. This conforms to the observation that nearly all lymphomas occurring in patients with Sjögren's syndrome are extrasalivary. Hematoxylin and eosin, ×40.

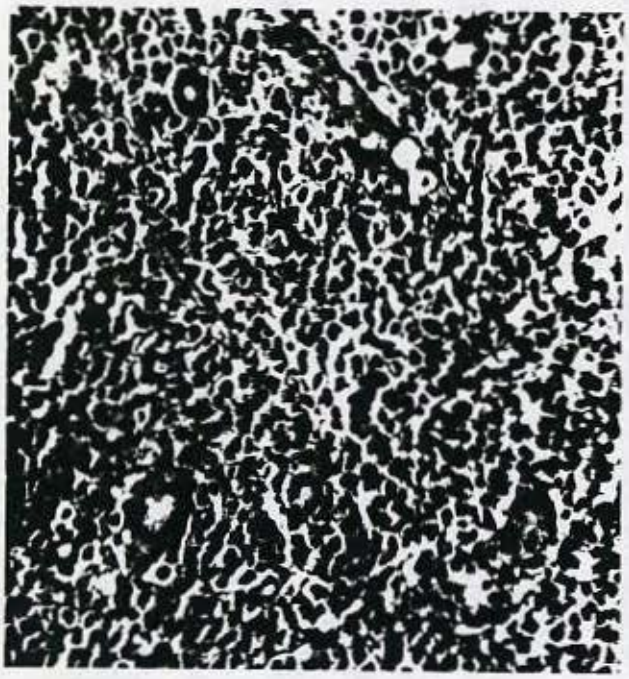

Figure 13. Higher magnification of the lymphoma shown in Figure 12. Hematoxylin and eosin, ×160.

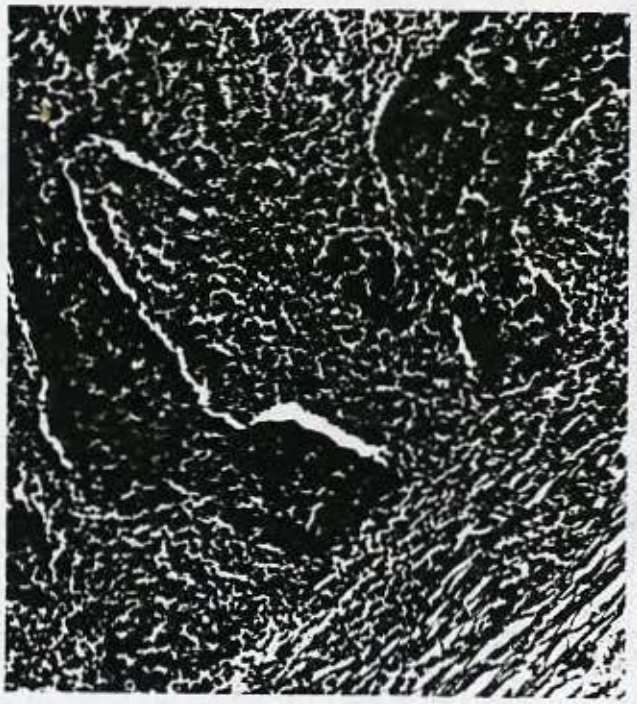

Figure 14. Carcinoma ex lymphoepithelial lesion. A poorly differentiated nonkeratinizing carcinoma still conforming to the shape of epimyoepithelial islands. Differential diagnosis must always exclude a metastasis to parotid lymph nodes. Hematoxylin and eosin, ×65.

auricular lymph nodes and later to supraclavicular and paratracheal nodes. Distant sites of metastasis include the liver and lungs.

PATHOGENESIS

Parts of the pathogenetic puzzle of Sjögren's syndrome are being assembled. These have been primarily genetic and immunologic factors, with each posing individual difficulties in interpretation. Data from in vivo and in vitro studies suggest three possibilities for the etiology of the syndrome:

(*A*) The disorder is based on a genetic abnormality of the immune system. For example, this may involve an abnormality of B cells in which there is a spontaneous B-cell activation, or possibly an abnormality of T cells in which excessive T-cell helper function or a depression of T-cell suppressor function permits or induces B-cell activation.

(*B*) The disorder results from an antigenic challenge, that is, an infection. The acquired antigenic stimulus may be a viral disease that alters surface antigens, which in turn stimulates B-cell activation and the production of antibodies.

(*C*) The disorder is an outcome of A and B, in which there is an interaction of an acquired exogenous stimulus with a specific genetic susceptibility to infection, or a genetic control of the response to the infective agent.

There is much to commend the C hypothesis. Current in vitro tests and animal models of research have almost exclusively been related to mononuclear cell infiltration and their immunoregulation in Sjögren's syndrome. These are certainly important, but any etiologic hypothesis must address the profound changes in the major and minor salivary glands, particularly the alterations of the salivary ducts.

Cytomorphologic changes in salivary duct cells occur in nearly all inflammatory and obstructive diseases of the salivary glands. However, the histologic repertoire of changes is limited, with the usual manifestations being mucous cell hyperplasia, squamous metaplasia, and an atrophic flattening. These are often accompanied by periductal acute and chronic inflammatory cells. Clinically, the patients exhibit unilateral or bilateral parotid enlargements which in turn divide into childhood and adult forms.[28] Spontaneous recovery occurs in both; in children it occurs at about the time of puberty. Only a small number evolve or are associated with Sjögren's syndrome. These patients present with the adult form of recurrent parotid swellings.[28] I know of no documented case in which the childhood form has progressed to Sjögren's syndrome. In adult patients who do not undergo spontaneous resolution conservative treatment is effective to some degree in 85% of cases.[28]

Despite similarities in histopathologic changes in salivary tissues, a patient who manifests Sjögren's syndrome is biologically different from the majority of patients with recurrent inflammatory disease of the salivary glands. Maynard's[28] collection of 300 patients confirms this. The patients do not have keratoconjunctivitis sicca, an associated arthritis, or abnormal serum proteins suggestive of an autoimmune process. Their disease is a local salivary gland disease without the striking predilection for females seen in Sjögren's syndrome. The suggestion that these patients have a less highly developed form of Sjögren's syndrome is unproven and not likely to be proven.

Results of testing for several antigenic determinants in patients with primary and secondary Sjögren's syndrome are presented in Table 4.[8] The different HLA-alloantigens indicate there is a genetic difference between the two forms of the syndrome. The findings of individual anti-B-cell antisera (Ia-172, Ia-350) point to the probability that a common immune response genetic component exists.[8]

Of great interest in the study of the pathogenesis of Sjögren's syndrome, particularly in the primary type, are such diseases as primary biliary cirrhosis[29] and chronic graft-vs-host disease.[30] Both have a prominent clinical sicca component and both have ductal epithelium as the apparent target structures. Chronic graft-vs-host disease has features of immune dysregulation, that is, hypergammaglobulinemia and lymphoplasmacellular infiltration of the viscera and lymph nodes.[30] Primary biliary cirrhosis is considered by some workers to be a "dry gland syndrome" with the clinical and pathologic findings not only of Sjögren's syndrome but also of graft-vs-host disease. Lacrimal and salivary glands are involved in 70% to 100% of patients and hyposecretion of the pancreas has also been described.[29]

Epstein and co-workers[29] have postulated that in primary biliary cirrhosis the observed duct lesions and disturbances of the immune system are a result of an immune response to the histocompatibility (HC) complex antigens, which are present in high density on biliary tract duct cells.

Table 4. HLA-Alloantigens and immune associated (Ia) antigens in Sjögren's syndrome *

Antigen	Primary Sjögren's syndrome	Secondary Sjögren's syndrome
HLA-B-8	Increased frequency	No increase
HLA-DRW3	Increased frequency	No increase
HLA-DRW4	No increase	Increased frequency
Ia-172	Increased frequency	Increased frequency
Ia-350	Increased frequency	Increased frequency

*From data presented by Moutsopoulos and co-workers.[8]

Such an immune response could be caused by altered antigenicity of epithelial cell HC antigens or by a failure of the HLA-dependent T-cell self-recognition system; in effect, a graft-vs-host process in which the newly antigenic duct cells serve as a "graft."

There is uncertainty over how widespread HC antigens are in normal tissue cells other than blood or lymphoid. Parr and Kirby,[31] using immunoferritin labeling studies, have shown that bile ducts, capillary endothelium, and pancreatic exocrine and duct cells possess HC antigens on their lateral and basal membranes. Parenchymal cells (hepatic and insular) expressed little or no labeling.

The predominance of HC antigen on duct cells, particularly those of an exocrine function, allows one to extend the graft-vs-host hypothesis to Sjögren's syndrome. Fig. 15 presents two possible pathogenic mechanisms of duct cell destruction in the salivary tissues. With the B mechanism, the duct cells are the primary targets of alloreactivity by virtue of the altered HC antigens on their membranes. With the C mechanism the duct cells are "hit" indirectly or only as "bystanders."[32] With the indirect mechanism a foreign protein (virus, antigen) has combined with a lymphocyte/monocyte to change HC antigenic structure. With either the B or C mechanism, a failure of T-cell and B-cell cooperation, usually by dysregulation of T-cell subsets, perpetuates the reaction and the lymphoid cell reaction in the salivary glands is enhanced by a recruitment of lymphocytes.[33-38] Interactions between sensitized lymphocytes and

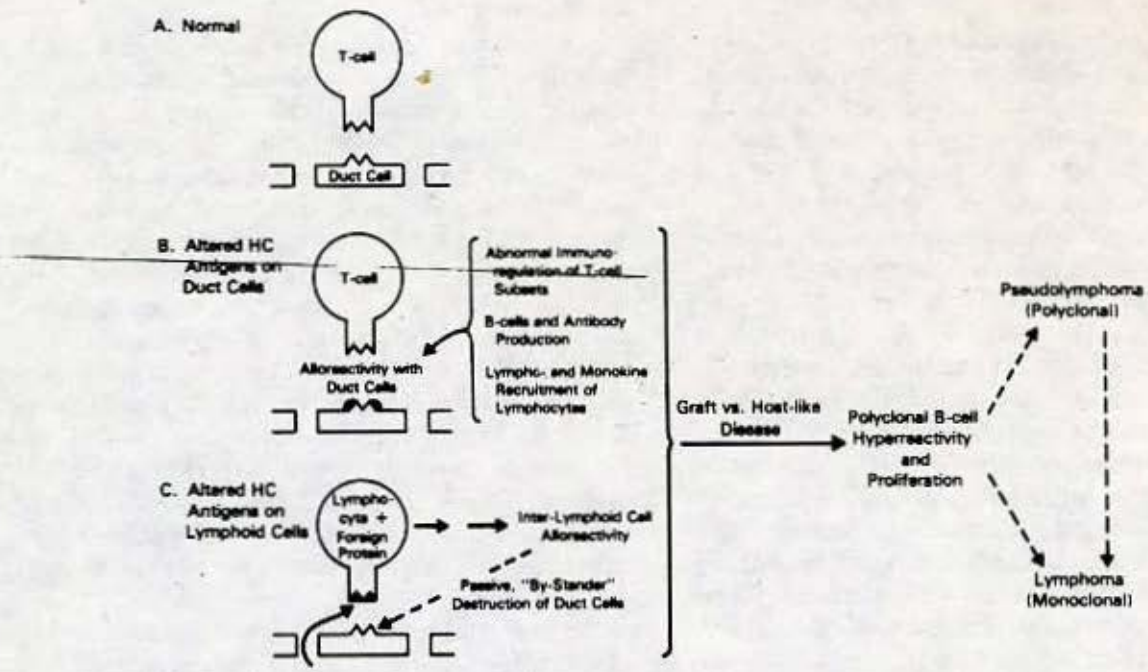

Figure 15. Mechanisms of salivary duct damage in Sjögren's syndrome. (A) represents the normal dynamic state of self-recognition. (B) and (C) present two possibilities of the sequence leading to ductal epithelium changes. In (B) the duct cells' HC antigens are changed so that their membranes are no longer recognized as self, thereby promoting a presumed direct hit. In (C) the duct damage is indirect by T-cell and B-cell interaction to antigens on lymphocytes combined with abnormal immunoregulation of T-cell subsets.

Table 5. Incidence of lymphomas in organ transplant recipients *

Incidence of all types of malignancy	2–13%
Percent of lymphomas	29%
Hodgkin's disease	2%
Non-Hodgkin's disease	98%
Histologic type of non-Hodgkin's lymphoma	60% large cell, B-cell lymphomas (reticulum cell sarcoma, immunoblastic sarcoma, histiocytic)
Organ involvement by lymphoma	53% localized
	47% regional and widespread
	41% central nervous system involvement

*From data presented by Penn.[43]

specific alloantigens lead to the elaboration of factors that induce lymphocytes to accumulate at the site of the alloreaction.[37,38] Unless checked, the graft-vs-host disease-like disorder continues and further destruction of exocrine parenchyma follows. Prolonged antigenic stimulation can also lead to a multistage process of polyclonal B-cell hyperreactivity with autoantibody production, systemic autoimmune disease, pseudolymphomatous tumors in extrasalivary tissues, and true lymphoma, but perhaps only in predisposed patients.

Whether one subscribes to the direct hit theory or to the theory of an indirect hit by an interlymphoid cell alloreactivity, the precipitating change is in the HC antigenic structure of cells. The altered antigens may belong to the major histocompatibility complex (MHC) or to minor, tissue-specific antigens.[39-41] How the HC antigens are changed is not known, but viral infection, either primary or secondary, in susceptible hosts may predispose them to such changes.

The viral theme is also found in evaluations of post-transplantation neoplasia. An increased incidence of de novo neoplasms has been reported in long-term survivors of organ transplantation. Penn and Starzl[42] have indicated the incidence of neoplasia to be 80 times greater than in the average population within a comparable age range. One factor thought to be responsible is the prolonged use of immunosuppressive drugs given to prevent rejection. Lymphomas are the most common nonepithelial neoplasms in transplant recipients (Table 5).[43] In a study of over 6,000 patients reported to a kidney transplant registry, Hoover and Fraumeni[44] calculated that the risk of developing lymphoma after transplantation was about 35 times higher than normal, and that this was due largely to a particularly enhanced risk of developing reticulum cell sarcoma, which was 350 times greater than expected. Skin and lip cancers occurred up to 4 times more often than expected and other neoplasms were 2.5 times more common.

Several factors are common in these patients: (*1*) heavy immunosuppression, (*2*) chronic allogenic stimulation, and (*3*) herpes virus infection (primary and reactivation types). The ubiquitous herpes virus can be latent for long periods of time, and most people are infected at some time during their lives. The virus is also oncogenic in animals, will transform cells in vitro, and is implicated in malignancies of the lymphoproliferative system, skin, and cervix, which are the very tumors most common in transplant recipients.[45]

Experimental evidence suggests the latent virus cannot be activated by immunosuppression alone, but requires antigenic stimulation for reactivation.[45] Once reactivated, viruses such as the Epstein-Barr virus (EBV) stimulate repeated cell division in B lymphocytes because these cells possess a specific receptor for the virus. This results in a polyclonal proliferation of B cells that is controlled by the action of suppressor T cells and EBV-specific antigens, such as in infectious mononucleosis. If suppressor cell activity is impaired, a conversion of the polyclonal lymphoproliferation to a monoclonal, uncontrolled lymphoma is possible.[45]

In Sjögren's syndrome the relatively high frequency of lymphoma is also characterized by a progression from a polyclonal B-cell growth to an overt monoclonal malignancy. Patients with the syndrome have an increased risk of lymphoma, as do patients with autoimmune diseases, primary immunodeficiency states, and allogeneic transplants. In each category, lymphoma is presumed to result from a selective emergence of a single clone produced by a cytogenic defect.

SUMMARY

A distinction should be made between the histopathologic diagnosis of lymphoepithelial lesion of salivary glands and the systemic disorder of

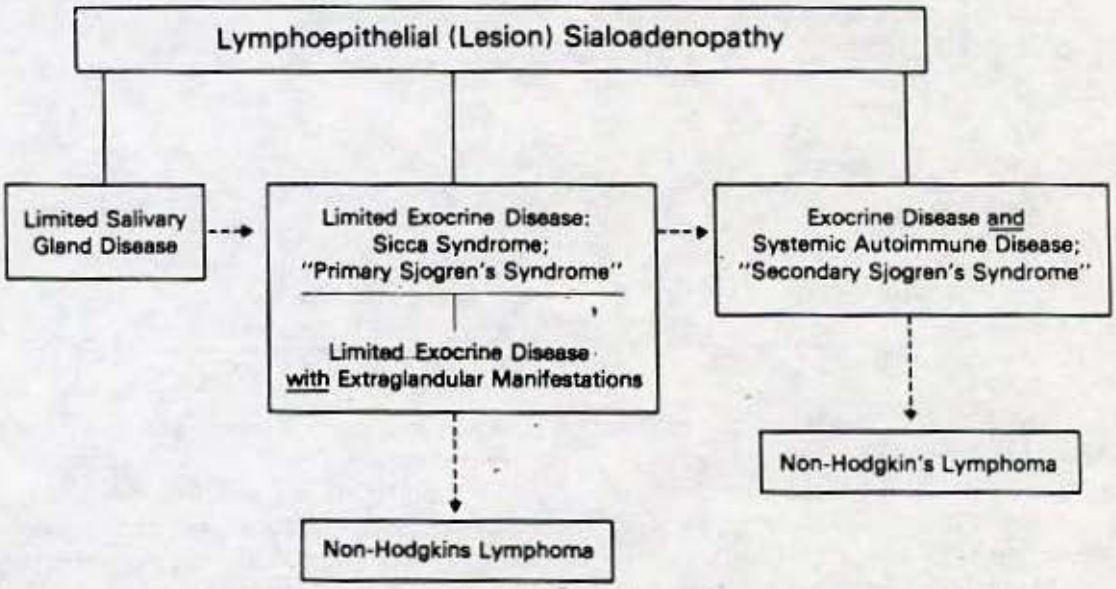

Figure 16. Relationship of the lymphoepithelial sialoadenopathy (lesion) to clinical manifestations.

Sjögren's syndrome. The latter can be a pleiotropic disorder with severe systemic manifestations, whereas the former need not be associated with the syndrome, even though it is the histologic hallmark of the syndrome in salivary tissues.

Sjögren's syndrome is best considered to be a disorder of altered immunoregulation in which there is a lymphocyte-mediated destruction of exocrine glandular epithelium. The lymphoepithelial lesion is a form of sialoadenopathy that reflects this gland destruction and it can be found in at least three clinicopathologic states (Fig. 16).

Pathogenically it is proposed that Sjögren's syndrome represents a graft-vs-host disease-like process in which histocompatibility antigens of ductal epithelium or lymphoid cells are changed so that self-recognition does not occur. Patients at risk are those with accompanying genetic abnormalities of T-cell and B-cell cooperation. In vitro tests, in vivo tests, and the high incidence of non-Hodgkin's lymphomas in patients with the syndrome provide clinical and laboratory support for this reasoning.

The next part of this series will consider the myoepithelial cell and its significance in salivary gland tumors.

REFERENCES

1. Ferlito A, Cattai N: The so-called "benign lymphoepithelial lesion." Part 1. Explanation of the term and its synonymous and related terms. *J Laryngol Otol* 94:1189–1197, 1980.
2. Seifert G, Donath K: Classification of the pathohistology of diseases of the salivary glands—review of 2,600 cases in the salivary gland register. *Beitraege Zur Pathologie* 159:1–32, 1976.
3. von Gumberz C, Seifert G: Immunoglobulin-containing plasma cells in chronic parotitis and malignant lymphomas of the parotid gland. Comparing immunocytochemical observations of frequency and localization. *Virchows Arch [Pathol Anat]* 389:79–92, 1980.
4. Hemenway WG: The parotid gland in Mikulicz disease and Sjögren's syndrome. *Ann Otol Laryngol* 69:849–867, 1960.
5. Hemenway WG: Chronic punctate parotitis. *Laryngoscope* 81:485–509, 1971.
6. Boquist L, Kumlien A, Ostberg Y: Ultrastructural findings in a case of benign lymphoepithelial lesion (Sjögren's syndrome). *Acta Otolaryngol* 70:216–226, 1970.
7. Kahn LB: Benign lymphoepithelial lesion (Mikulicz's disease) of the salivary gland: An ultrastructural study. *Hum Pathol* 10:99–104, 1979.
8. Moutsopoulos HM, Chused TM, Mann DL, Klippel JH, Fauci AS, Frank MM, Lawley TJ, Hamburger MI: Sjögren's syndrome (sicca syndrome): Current issues. *Ann Intern Med* 92:212–226, 1980.
9. Strand V, Talal N: Advances in the diagnosis and concept of Sjögren's syndrome (autoimmune exocrinopathy). *Bull Rheum Dis* 30:1046–1052, 1980.
10. Snider GL: Case 28-1975, in Case Records of the Massachusetts General Hospital. *N Engl J Med* 293:136–144, 1975.
11. Batsakis JG, Howard DR: Sjögren's syndrome: An immune response associated disorder. *Clinical Laboratory Annual* 1:171–188, 1982.
12. Kassan SS, Gardy M: Sjögren's syndrome: An update and overview. *Am J Med* 64:1037–1046, 1978.
13. Moutsopoulos HM, Fauci AS: Immunoregulation in Sjögren's syndrome. Influence of serum factors on T-cell subpopulations. *J Clin Invest* 65:519–528, 1980.

14. Friedman H, Kilmar V, Galletta VP, Cossermelli W: Lip biopsy in connective tissue diseases. A review and study of seventy cases. *Oral Surg* 47:256–262, 1979.
15. Greenspan JS, Daniels TE, Talal N, Sylvester RA: The histopatholgoy of Sjögren's syndrome in labial salivary gland biopsies. *Oral Surg* 37:217–229, 1974.
16. Tarpley TM, Anderson LG, White CL: Minor salivary gland involvement in Sjögren's syndrome. *Oral Surg* 37:64–74, 1974.
17. Eisenbud L, Platt N, Stern M, D'Angelo W, Sumner P: Palatal biopsy as a diagnostic aid in the study of connective tissue diseases. *Oral Surg* 35:642–648, 1973.
18. Chisholm DM, Waterhouse JP, Mason DK: Lymphotytic sialadenitis in the major and minor glands: A correlation in postmortem subjects. *J Clin Pathol* 23:690–694, 1970.
19. Sale GE, Shulman HM, Schubert MM, Sullivan KM, Kopecky KJ, Hackman RC, Morton TH, Storb A, Thomas ED: Oral and ophthalmic pathology of graft versus host disease in man: Predictive value of the lip biopsy. *Hum Pathol* 12:1022–1030, 1981.
20. Nessan VJ, Jacoway JR: Biopsy of minor salivary glands in the diagnosis of sarcoidosis. *N Engl J Med* 301:922–924, 1979.
21. Batsakis JG, Bernacki EG, Rice DH, Stebler ME: Malignancy and the benign lymphoepithelial lesion. *Laryngoscope* 85:389–399, 1975.
22. Ferlito A, Cattai N: The so-called "benign lymphoepithelial lesion." Part II. Clinical and pathological considerations with regard to evolution. *J Laryngol Otol* 94:1283–1301, 1980.
23. Anderson LG, Talal N: The spectrum of benign to malignant lymphoproliferation in Sjögren's syndrome. *Clin Exp Immunol* 9:199–221, 1971.
24. Banks PM, Witrak GA, Conn DL: Lymphoid neoplasia following connective tissue disease. *Mayo Clin Proc* 54:104–108, 1979.
25. Zulman J, Jaffe R, Talal N: Evidence that malignant lymphoma of Sjögren's syndrome is a monoclonal B-cell neoplasm. *N Engl J Med* 299:1215–1220, 1978.
26. Diaz-Jouanen E, Ruiz-Arguelles J, Vega-Ortiz JM, Villareal G, Alarcon-Sequvia D: From benign polyclonal to malignant monoclonal lymphoproliferation in a patient with primary Sjögren's syndrome. *Arthritis Rheum* 24:850–853, 1981.
27. Redondo C, Garcia A, Vazquez F: Malignant lymphoepithelial lesion of the parotid gland. Poorly differentiated squamous cell carcinoma with lymphoid stroma. *Cancer* 48:289–292, 1981.
28. Maynard J: Recurrent swellings of the parotid gland, sialectasis and Mikulicz's syndrome. *J R Soc Med* 72:591–598, 1979.
29. Epstein O, Thomas HC, Sherlock S: Primary biliary cirrhosis is a dry gland syndrome with features of chronic graft versus host disease. *Lancet* i:1166–1168, 1980.
30. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, Hackman R, Tsoi M-S, Storb R, Thomas ED: Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med* 69:204–217, 1980.
31. Parr EL, Kirby WN: An immunoferritin labeling study of H-2 antigens on dissociated epithelial cells. *J Histochem Cytochem* 27:1327–1336, 1979.
32. Elson CO, Reilly RW, Rosenberg IH: Small intestinal injury in the graft versus host reaction: An innocent bystander phenomenon. *Gastroenterology* 72:886–889, 1977.
33. Dosch H-M, Gelfand EW: Failure of T and B cell cooperation during graft-versus-host disease. *Transplantation* 31:48–50, 1981.
34. Parks DE: Cellular mechanisms of tolerance to self. *Clinical Immunology Allergy* 1:3–16, 1981.
35. McDevitt HO: Regulations of the immune response by the major histocompatibility system. *N Engl J Med* 303:1514–1517, 1980.
36. Reinherz EL, Parkman R, Rappeport J, Rosen FS, Schlossman SF: Aberrations of suppressor T cells in human graft-versus-host disease. *N Engl J Med* 300:1061–1067, 1979.
37. Hoffman RA, Ascher NL, Simmons RL: Migratory behavior of lymphocytes during allograft rejection. *Transplant Proc* 8:1102–1104, 1981.
38. Hopt UT, Sullivan W, Simmons RL: Recruitment of lymphocytes to sponge matrix allografts. *Transplant Proc* 8:1086–1090, 1981.
39. Lalezari P: Organ-specific and systemic alloantigens: Interrelationships and biologic implications. *Transplant Proc* 12 (Suppl. 1):12–21, 1980.
40. Lee HM, Waldrep JC, Mendez-Picon G, Mohanakumar T: Antibodies eluted from rejected human renal allografts: specificity to B lymphocytes, monocytes, primary kidney cells, and endothelial cells. *Transplant Proc* 13:108–110, 1981.
41. Matsunaga T, Ohno S: Cellular immune response to non-MHC plasma membrane antigens. *Transplant Proc* 12 (Suppl. 1):135–140, 1980.
42. Penn I, Starzl TE: Malignant tumors arising de novo in immunosuppressed organ transplant recipients. *Transplant Proc* 14:407–417, 1972.
43. Penn I: Malignant lymphomas in organ transplant recipients. *Transplant Proc* 8:736–738, 1981.
44. Hoover R, Fraumeni JF: Risk of cancer in renal transplant recipients. *Lancet* ii:55–57, 1973.
45. Thiru S, Calne RY, Nagington J: Lymphoma in renal allograft patients treated with Cyclosporin-A as one of the immunosuppressive agents. *Transplant Proc* 13:359–364, 1981.

Case 2. Terminal duct (polymorphous low-grade) adenocarcinoma, palate

The histologic appearance and spectrum of this principally oral cavity salivary adenocarcinoma are presented in the two accompanying reprints. It is my impression that this carcinoma is the second most common salivary carcinoma in the oral cavity; exceeded only by the adenoid cystic carcinoma. Its histogenetic derivation from the terminal ducts accounts for the variable differentiation seen in the tumors and also for the variable myoepithelial cell participation. It is characteristically low-grade despite often prominent small nerve invasion and extension into adjacent bone.

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Adenocarcinomas of the oral cavity:
A clinicopathologic study of terminal duct carcinomas

by

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Introduction

The reported incidence of malignant salivary gland tumors in the oral cavity has varied according to the referral pattern of the authors' institution (Chaudhry *et al.*, 1961; Epker and Henny, 1969; Fine *et al.*, 1960; Luna *et al.*, 1968; Vellios and Shafer, 1959) (Table I). It is reasonable to assume, however, that there is a nearly equal incidence of benign and malignant variants. Of a total of 1,965 oral salivary gland tumors, 52 per cent were classified as benign and 48 per cent as malignant (Gates, 1972). Forty-two per cent of the latter were adenoid cystic carcinomas. Mixed tumors (pleomorphic adenomas) made up 92 per cent of the benign tumors. Such a numerical dominance by these two types of salivary gland neoplasia has led to their use as paradigms and, in the event, has obscured recognition and reporting of other, less often encountered neoplasms, e.g. the adenocarcinomas.

A clinico-pathologic evaluation of adenocarcinomas of salivary tissues has also been delayed by their inclusion under the generic heading of 'adenocarcinoma', wherein all forms of glandular malignancy are included, or by being placed in the category of 'adenocarcinoma, not otherwise specified'. Adenocarcinomas are, however, distinctive neoplasms which may be sub-classified according to their tissue growth patterns or histo-cytomorphology. Table II presents a classification of adenocarcinoma which is applicable to both major or minor salivary glands.

In this report, we present a study of 12 patients with a hitherto undescribed variant of adenocarcinoma of the oral cavity—*the terminal duct carcinoma.*

Report of Cases

A summary of the 12 cases is presented in Table III. Eleven of the 12 were from the consultation service of the senior author. Case 4 represents a patient treated at The University of Texas M. D. Anderson Hospital. Eight of the patients were women. The age of the patients at the time of surgery ranged from 26 to 65 years. Two patients (cases 3 and 5) gave a history of an antecedent lesion removed from the palate 12 and 8 years earlier.

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TABLE I
FREQUENCY OF MALIGNANCY OF INTRAORAL SALIVARY GLAND TUMORS

Authors	No. of tumors	Per cent malignant
Vellios and Shafer (1959)	54	54
Fine *et al.* (1960)	79	47
Chaudhry *et al.* (1961)	94	54
Epker and Henny (1969)	90	70
Luna *et al.* (1968)	68	81

The palate, usually at the junction of the soft and hard palate, was the primary site in five patients.

The clinical presentation was that of a painless mass, covered with an intact mucosa in all patients. The size of the tumors ranged from 1.5 cm. to 5.0 cm. in major dimension. The largest tumor presented in the base of the tongue.

TABLE II
HISTOPATHOLOGIC CLASSIFICATION OF ADENOCARCINOMAS OF SALIVARY TISSUES

Papillary adenocarcinoma (with or without mucus production)
Mucoid (colloid) adenocarcinoma
Clear cell carcinomas (epithelial-myoepithelial carcinoma of intercalated duct origin)
Ductal carcinomas
Terminal duct carcinomas
Poorly differentiated and undifferentiated adenocarcinoma
Neuroendocrine carcinomas
(a) Adenocarcinoma with neuroendocrine differentiation
(b) "Oat cell", carcinoid

A form of salivary gland adenoma was the original histopathologic diagnosis in 7 of 12 tumors. A diagnosis of adenoid cystic carcinoma was made in three patients. In every instance, the contributing pathologist expressed doubt over his diagnosis.

Surgical excision was the primary treatment in all patients. The extent of the excision ranged from 'excisional biopsy' to a bloc resection, including hemimandibulectomy in three patients (cases 8, 9 and 10). Four patients (cases 1, 6, 8 and 10) also underwent a radical neck dissection. No histologically positive nodes were found. Two patients received post-operative irradiation (cases 1 and 10).

Invasion of bone was evident in three cases and presumed in one.

All of the patients are alive and without clinical recurrence of their neoplasm, but the follow-up period has been short; one month to two and one-half years.

Histopatholgic Findings

The light-optic appearance of the terminal duct adenocarcinomas was remarkably similar in all cases. Figures 1–6 are not only representative, they are prototypical.

A deceptive circumscription was present in nearly every case but a complete capsule was never present. An infiltrative growth pattern was always present. Infiltration was either by single ducts (particularly beneath the mucosa or into adjacent salivary tissue) or by groups of neoplastic ducts and solid epithelial

TABLE III
SUMMARY OF CASES

Case	Sex-age	Site	Original diagnosis	Invasion of nerve	Invasion of bone
1.	F-47	Palate	Adenoid cystic carcinoma	+	–
2.	M-56	Palate	Malignant mixed tumor	+	–
3.	F-46	Palate	Pleomorphic adenoma	+	+
4.	F-49	Palate	Adenoid cystic carcinoma	+	–
5.	F-26	Palate	Monomorphic adenoma	+	–
6.	M-59	Base of tongue	Monomorphic adenoma	+	–
7.	M-38	Base of tongue	Monomorphic adenoma	+	–
8.	F-32	Posterior trigone	Monomorphic adenoma	+	+
9.	F-41	Retromolar pad	Adenocarcinoma	+	–
10.	M-63	Anterior mandibular mucosa	Adenoid cystic carcinoma	+	+
11.	F-39	Upper lip	Monomorphic adenoma	+	–
12.	F-65	Buccal mucosa	Monomorphic adenoma	+	–

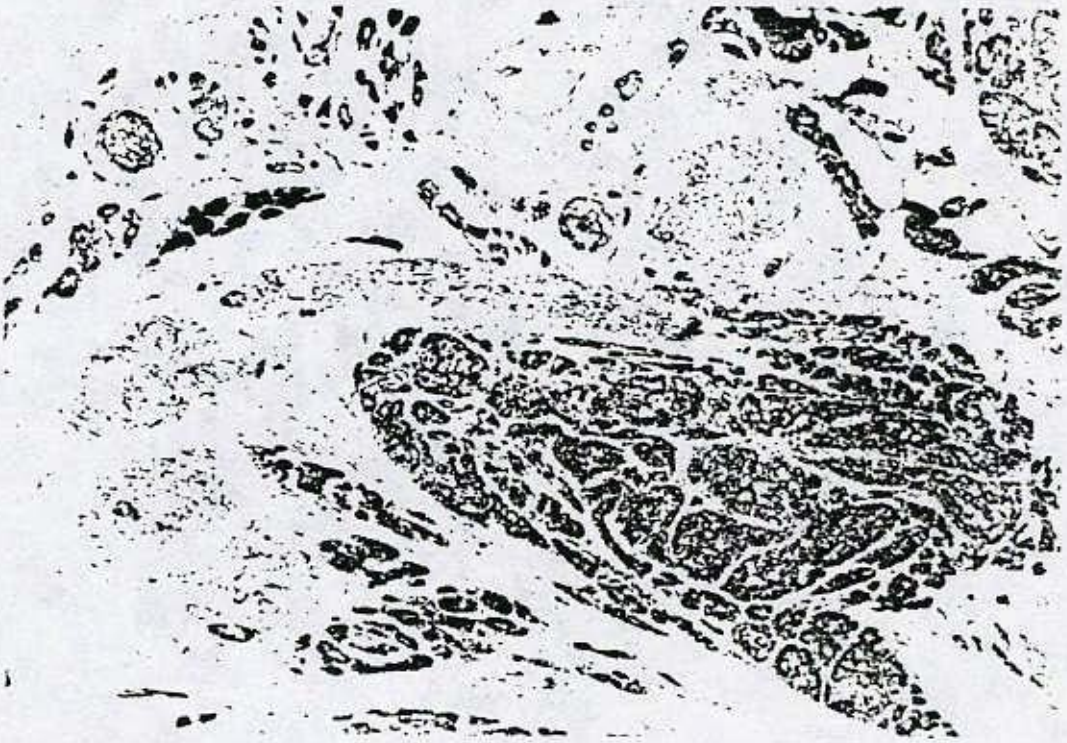

FIG. 1

Intraoral terminal duct carcinoma. Note the apparent multifocal origin and relation to nerves. Hematoxylin and eosin ×20.

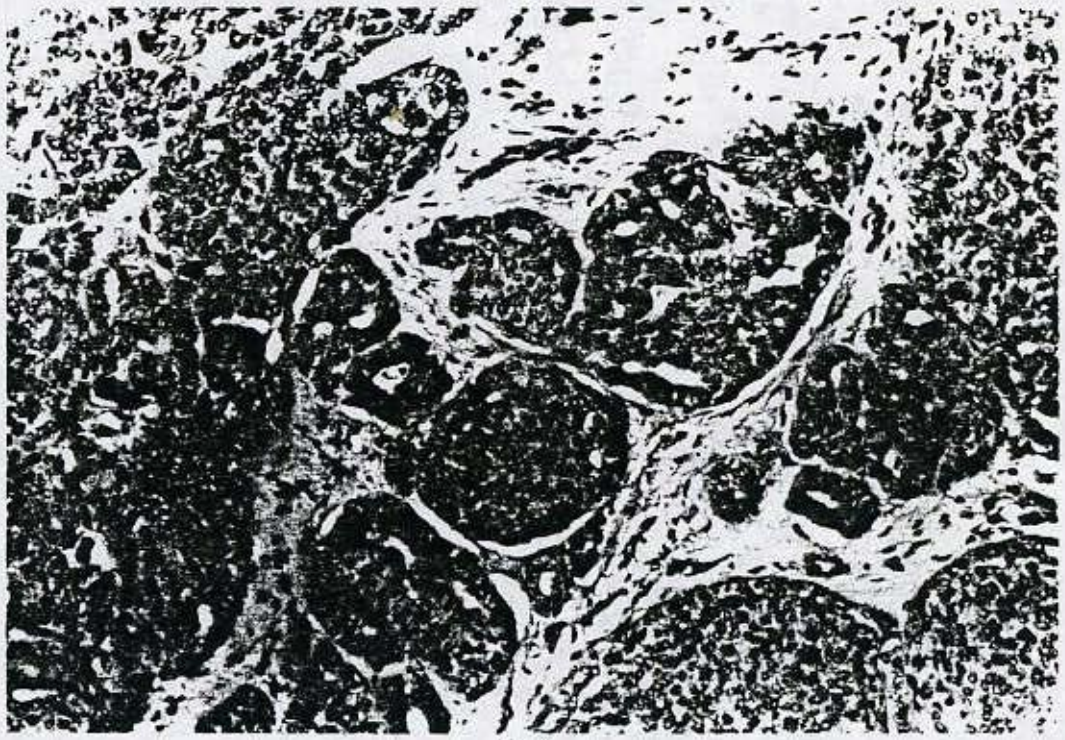

FIG. 2

Ductular and solid epithelial components of terminal duct carcinoma. Hematoxylin and eosin ×200.

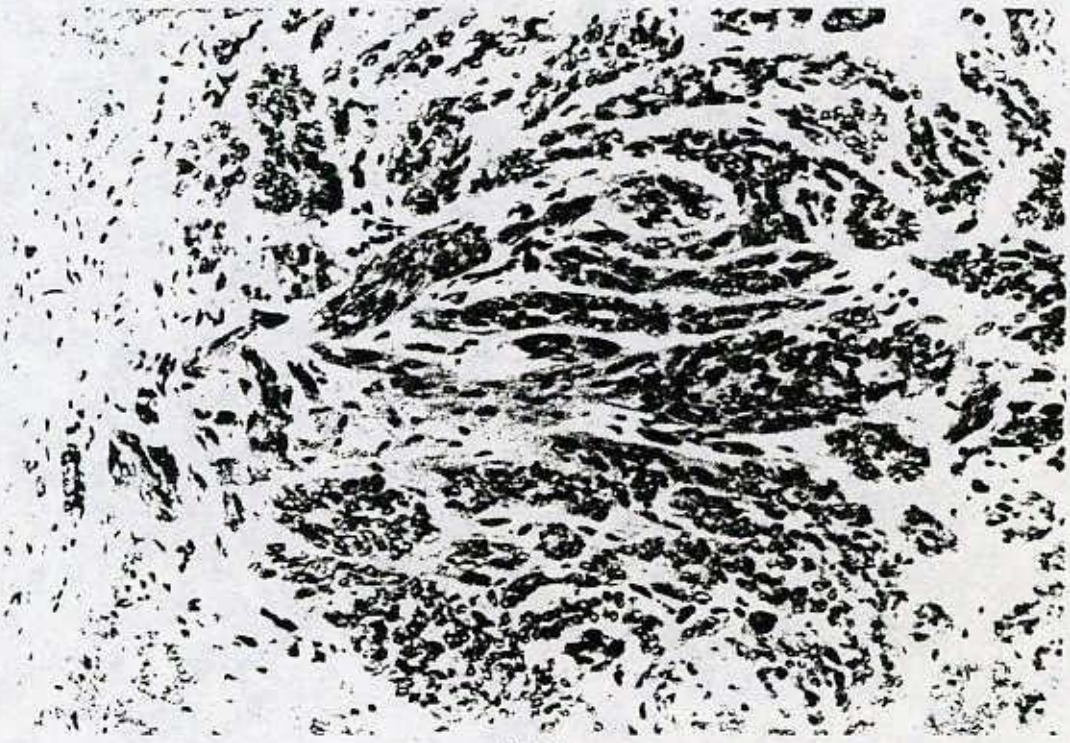

FIG. 3

Small ducts, spindle cells, and characteristic interepithelial stroma found in terminal duct carcinomas. Hematoxylin and eosin ×250.

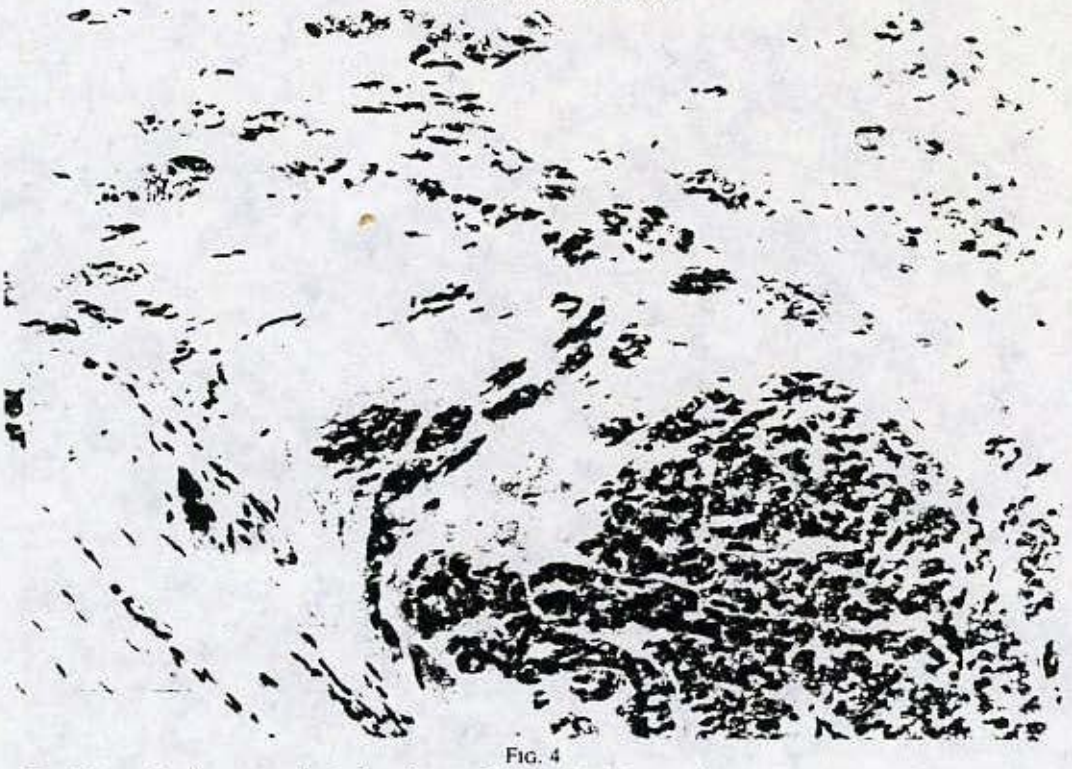

FIG. 4

Typical mucohyaline stroma that is found in areas of a terminal duct carcinoma. Hematoxylin and eosin ×180.

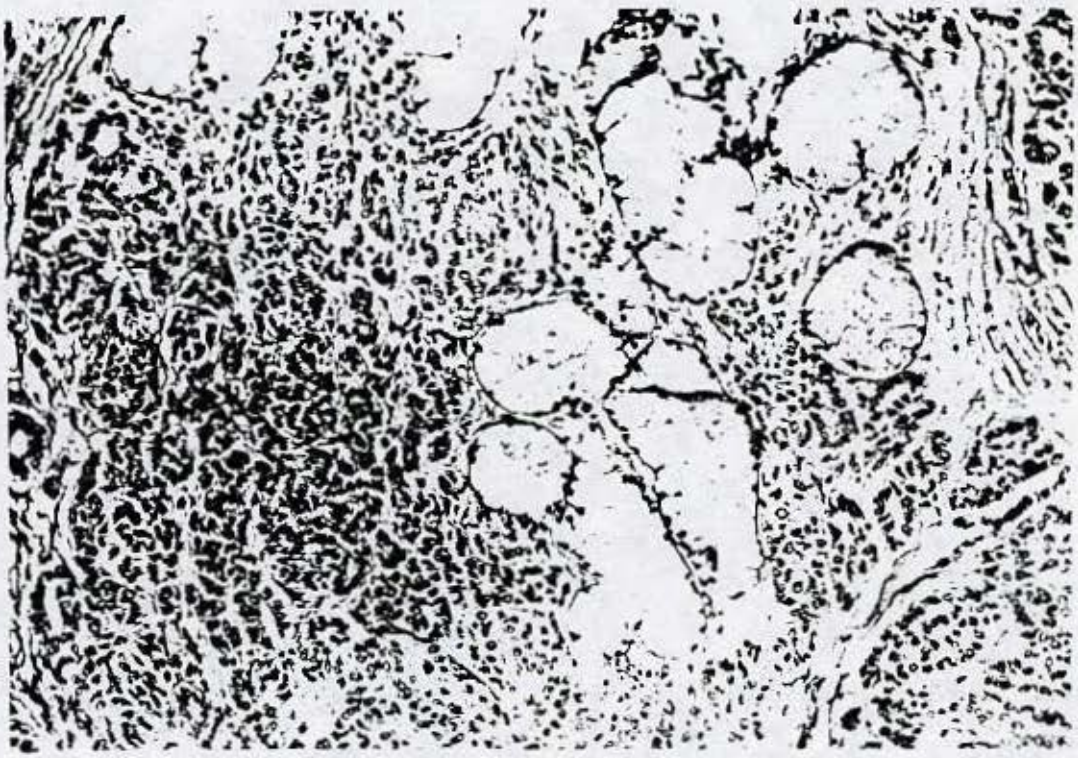

FIG. 5

Invasion of normal mucinous acini by terminal duct carcinoma. Hematoxylin and eosin ×180.

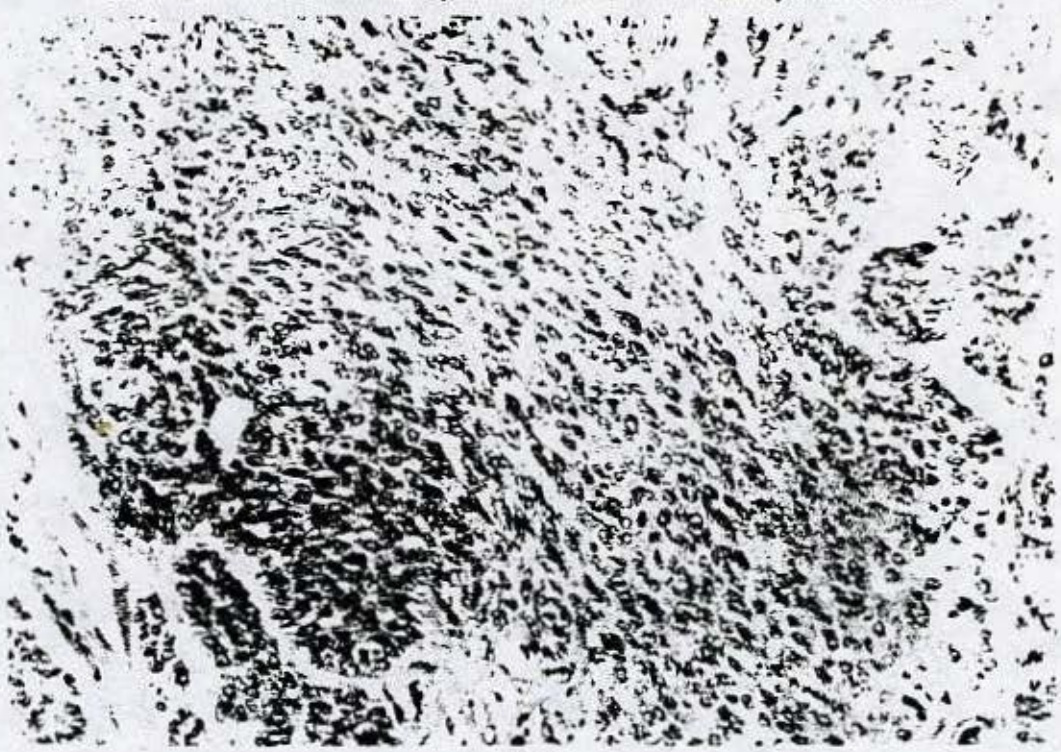

FIG. 6

Spindle cell area in a terminal duct carcinoma. By light optic and electron optic study, the cells manifest myoepithelial differentiation. Hematoxylin and eosin ×200.

TABLE IV
RELATIVE FREQUENCY OF NON-EPIDERMOID MALIGNANCY: SINO-NASAL TRACT*

	Per cent of all malignancy at site		
	Nasal cavity	Antrum	Other sinuses
Adenocarcinoma	9	6	20
Salivary type carcinoma	1.3	1.7	3.3
Melanoma	3	0.5	0.8
Olfactory neuroblastoma	0.7'	0.0	0.0
Lymphoma	2	1.6	2.1
Sarcoma	2.6	2.9	2.5

* Modified from Muir and Nectoux (1980).

the data in Table IV (Muir and Nectoux, 1980). In the oral cavity (Table V) nearly one-quarter of salivary gland tumors are adenocarcinomas (Chaudhry *et al.*, 1961; Epker and Henny, 1969; Hendrick, 1964; Reynolds *et al.*, 1966; Spiro *et al.*, 1973). This incidence is to be compared to that of mucoepidermoid carcinomas (Table VI and carcinomas ex pleomorphic adenoma (Table VII). Such data place adenocarcinomas second only to adenoid cystic carcinomas in the oral cavity. Table VIII amplifies this position in its presentation of 1221 salivary gland tumors of the palate (Chaudhry *et al.*, 1961; Coates *et al.*, 1975; Crocker *et al.*, 1970; Epker and Henny, 1969; Hjertman and Eneroth, 1970; Soskolkne *et al.*, 1973; Spiro *et al.*, 1973).

TABLE V
ADENOCARCINOMA OF THE ORAL CAVITY

Authors	No. salivary gland tumors	No. adeno-carcinomas	(%)
Spiro *et al.* (1973)	345	92	(27)
Chaudhry *et al.* (1961)	94	27	(18)
Epker and Henny (1969)	90	26	(18)
Hendrick (1964)	44	10	(23)
Reynolds *et al.* (1966)	31	6	(20)
	604	141	(23)

TABLE VI
MUCOEPIDERMOID CARCINOMAS OF THE ORAL CAVITY

Authors	No. salivary gland tumors	No. muco-epidermoid carcinomas	(%)
Spiro *et al.* (1973)	345	55	(13)
Chaudhry *et al.* (1961)	94	10	(10.6)
Epker and Henny (1969)	90	3	(15.5)
Hendrick (1964)	44	3	(7)
Reynolds *et al.* (1966)	31	4	(13)
	604	86	(14.2)

TABLE VII
CARCINOMA EX PLEOMORPHIC ADENOMA OF THE ORAL CAVITY

Authors	No. salivary gland tumors	No. carcinomas ex pleo-morphic adenoma	(%)
Spiro *et al.* (1973)	345	11	(3.2)
Chaudhry *et al.* (1961)	94	3	(3.2)
Epker and Henny (1969)	90	0	(0)
Hendrick (1964)	44	8	(18)
	573	22	(4.0)

The majority of the *adenocarcinomas* of salivary tissues are presumed to arise from the reserve cells of the metabolically active or conduit parts of the salivary duct unit, i.e., intra-, inter-, and excretory ducts (Fig. 10). The histogenesis of the terminal duct adenocarcinomas, however, resides in the neoplastic expression of the reserve cells of the intercalated ducts; sharing this origin with the tumors listed in Figure 10 (Batsakis, 1980b; Eversole, 1971).

Within the group of tumors arising from the intercalated ducts, there is a rather wide range of biologic behavior, but the clinical course of terminal duct adenocarcinomas is

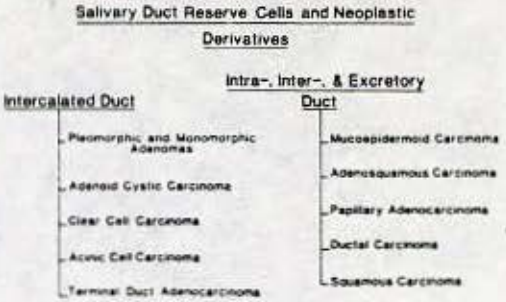

FIG. 10

TABLE VIII

SALIVARY TUMORS OF PALATE: HISTOLOGIC CLASSIFICATION*

Histologic type	Number of tumors	Per cent	Per cent of total
Benign	*625*		
Mixed tumor	573	92	47
Others	52	8	4.2
Malignant	*596*		
Adenoid cystic carcinoma	274	46	22
Adenocarcinoma	143	24	12
Mucoepidermoid carcinoma	120	20	10
Carcinoma ex pleomorphic adenoma	45	7.5	3.7
Acinous cell carcinoma	7	1.2	0.6
Undifferentiated	7	1.2	0.6
Miscellaneous	—	0.1	—

* Data assembled from the reports by Chaudhry *et al.*, 1961; Coates *et al.*, 1975; Crocker *et al.*, 1970; Epker and Henny, 1969; Hjertman and Eneroth, 1970; Soskolne *et al.*, 1973; Spiro *et al.*, 1973.

akin to that of adenoid cystic carcinoma. Both carcinomas manifest a significant neurotropism, local invasion of adjacent structures, and a low incidence of metastases to regional lymph nodes. The sharing of these clinical and pathologic characteristics raises the possibility that terminal duct carcinomas are only histopathologic variants of adenoid cystic carcinomas. This has been carefully considered by the present authors and cannot be confirmed. Although there is a considerable breadth of histologic expression attributed to adenoid cystic carcinoma (tubular, cribriform, cylindromatous, solid),

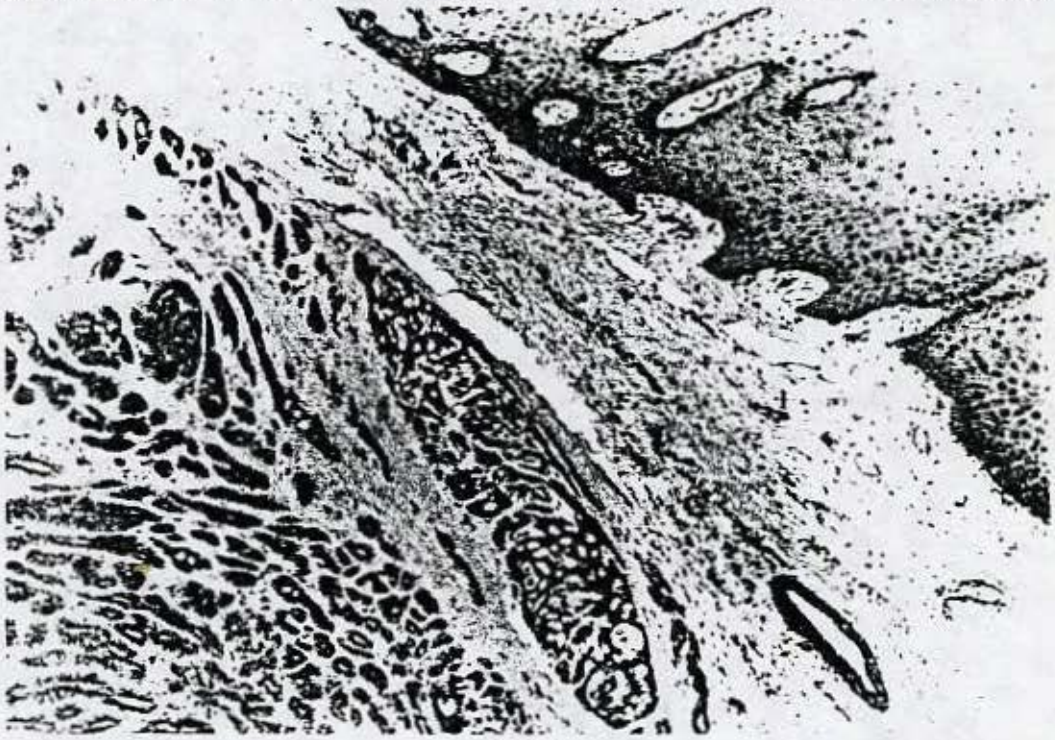

FIG. 11

Focally circumscribed terminal duct carcinoma beneath palatal mucosa. Superficial biopsy specimen from areas such as this can be misdiagnosed as a pleomorphic adenoma. Hematoxylin and eosin ×80.

none of the terminal duct carcinomas could be placed within the spectrum.

As judged by the original diagnoses, monomorphic and pleomorphic adenomas posed problems in differential diagnosis. Indeed, superficial biopsy specimens containing lobules with a mucohyaline matrix can simulate adenomas (Fig. 11). The often deceptively benign cytomorphology of the cells and their ductal arrangement may also mislead the examiner to a diagnosis of monomorphic adenoma (Batsakis *et al.*, 1981). Peripheral infilitrative growth, spindle cell areas and most of all, invasion of nerves, eliminate a diagnosis of monomorphic adenoma.

The authors have seen a similar small duct carcinoma as the malignant component of some carcinomas ex pleomorphic adenoma in major and minor salivary glands. In none of our 12 tumors, however, could we find histologic evidence of a precursor or maternal mixed tumor. Nor did we have the impression that the carcinoma had 'over-run' a mixed tumor.

The spindle cells in these terminal duct carcinomas are quite suggestive of a myoepithelial cell component and electron-optic study of fresh tissue from the tumor of patient 9 demonstrated myoepithelial differentiation in the spindle cells. Should this be further substantiated, terminal duct carcinomas are likely related to the clear cell class of salivary neoplasia: specifically, the epithelial-myoepithelial carcinoma of intercalated ducts. As can be seen from Figure 12, however, the outer clear cell mantle, often glycogen-rich, of the clear cell carcinoma distinguishes it from the carcinomas of the present report (Batsakis, 1980a; Corio *et al.*, 1982; Donath *et al.*, 1972).

A two and one-half year follow-up period is not sufficient to be able to delineate the full biologic potential of terminal duct carcinomas. The apparent local control in our patients, over the short post-operative

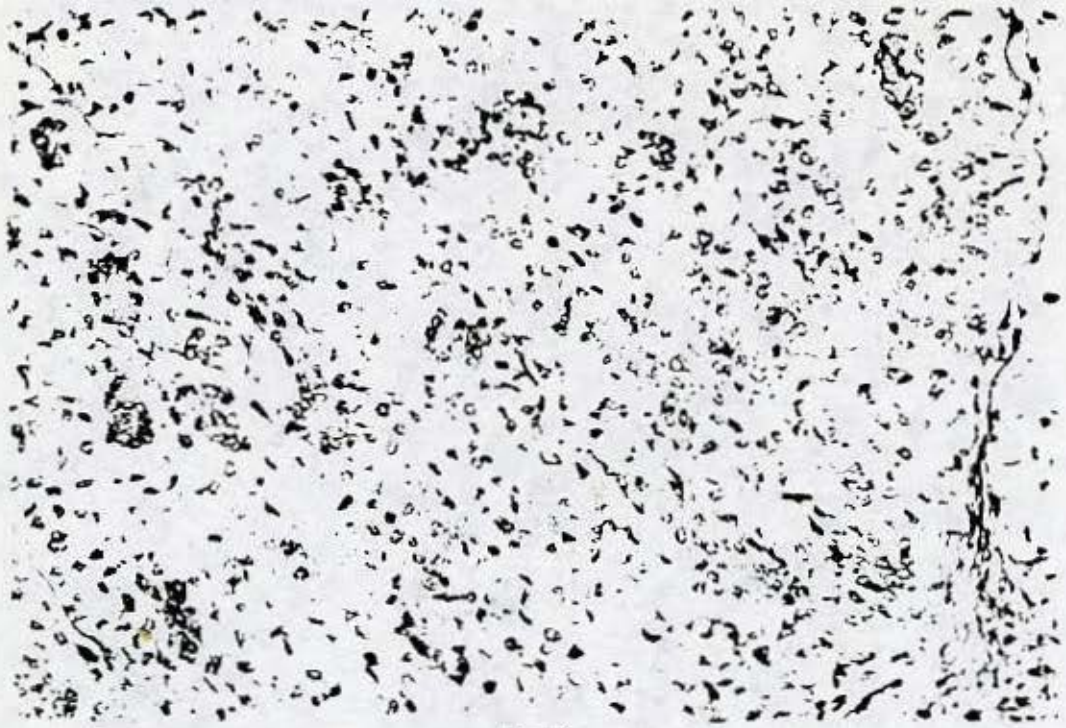

FIG. 12

Epimyoepithelial carcinoma of intercalated ducts. This clear cell carcinoma is likely related to the terminal duct carcinoma. Hematoxylin and eosin ×180.

interval is likely deceptive. Based on the present series, we would judge terminal duct adenocarcinomas to have a clinical course not unlike adenoid cystic carcinomas.

Summary

A clinico-pathologic study of 12 patients, each harboring a hitherto not delineated adenocarcinoma of salivary origin is presented. The authors have designated this histologically unique carcinoma as 'terminal duct adenocarcinoma' in deference not only to its light-optic appearance, but also to a putative origin from the reserve cells (epithelial and myoepithelial) of the intercalated duct. The tumors' local invasive properties with extension into nerves and adjacent bone suggest their biologic behavior is like that of adenoid cystic carcinomas.

References

BATSAKIS, J. G. (1980a). Clear cell tumors of salivary glands. *Annals of Otology, Laryngology and Rhinology*, **89:** 196–197.

BATSAKIS, J. G. (1980b). Salivary gland neoplasia: An outcome of modified morphogenesis and cytodifferentiation. *Oral Surgery, Oral Medicine, Oral Pathology*, **6:** 129–143.

BATSAKIS, J. G., BRANNON, R. B., and SCIUBBA, J. J. (1981) Monomorphic adenomas of major salivary glands: A histologic study of 96 tumours. *Clinical Otolaryngology*, **6:** 129–43.

CHAUDHRY, A. P., VICKERS, R. A., and GORLIN, R. J. (1961) Intraoral minor salivary gland tumors. *Oral Surgery, Oral Medicine, Oral Pathology*, **14:** 1194–1226.

COATES, H. L. C., DEVINE, K. D., DESANTO, L. W., and WEILAND, L. H. (1975). Glandular tumors of the Palate. *Surgery, Gynecology and Obstetrics*, **140:** 589–593.

CORIO, R. L., SCIUBBA, J. J., BRANNON, R. B., and BATSAKIS, J. G. (1982) Epithelial myoepithelial carcinoma of intercalated duct origin. *Oral Surgery, Oral Medicine, Oral Pathology*, **53:** 280–287.

CROCKER, D. J., CAVALARIS, C. J., and FINCH, R. (1970) Intraoral minor salivary gland tumors. Report of thirty-eight cases. *Oral Surgery, Oral Medicine, Oral Pathology*, **29:** 60–68.

DONATH, K., SEIFERT, G., and SCHMITZ, R. (1972) Zur Diagnose und Ultrastruktur des tubularen Speichelgangcarcinoms: epithelial-myoepitheliales Schaltstuckcarcinom. *Virchows Archivs (Pathol. Anat.)*, **356:** 16–31.

EPKER, E. B., and HENNY, F. A. (1969) Clinical, histopathologic and surgical aspects of intraoral minor salivary gland tumors, review of 90 cases. *Journal of Oral Surgery*, **27:** 792–804.

EVERSOLE, L. R. (1971) Histogenic classification of salivary gland tumors. *Archives of Pathology*, **92:** 433–443.

FINE, G., MARSHALL, R. B., and HORN, R. C. (1960) Tumors of the minor salivary glands. *Cancer*, **13:** 653–669.

GATES, G. A. (1972) Minor salivary gland tumors of the oral cavity. *Otolaryngologic Clinics of North America*, **5:** 283–289.

HENDRICK, J. W. (1964) The treatment of tumors of minor salivary glands. *Surgery, Gynecology and Obstetrics*, **118:** 101–111.

HJERTMAN, L., and ENEROTH, C. M. (1970) Tumors of the palate. *Acta Otolaryngologica Scandinavica*, **263:** 179–182.

LUNA, M. A., STIMSON, P. J., and BARDWILL, J. M. (1968) Minor salivary gland tumors of the oral cavity. *Oral Surgery, Oral Medicine, Oral Pathology*, **25:** 71–86.

MUIR, C. S., and NECTOUX, J. (1980) Descriptive epidemiology of malignant neoplasms of nose, nasal cavities, middle ear and accessory sinuses. *Clinical Otolaryngology*, **5:** 195–211.

REYNOLDS, C. T., MC AULEY, R. L., and ROGERS, W. P. (1966) Experience with tumors of minor salivary glands. *American Journal of Surgery*, **111:** 168–174.

SOSKOLNE, A., SELA, J., BEN-AMAR, A., and ULMANSKY, M. (1973) Minor salivary gland tumors: A survey of 64 cases. *Journal of Oral Surgery*, **31:** 528–531.

SPIRO, R. H., KOSS, L. G., HAJDU, S. I., and STRONG, E. E. (1973) Tumors of minor salivary origin. A clinicopathologic study of 492 cases. *Cancer*, **31:** 1117–129.

STENE, T., and KOPPANG, H. S. (1981) Intraoral adenocarcinomas. *Journal of Oral Pathology*, **10:** 216–225.

VELLIOS, F., and SHAFER, W. G. (1959) Tumors of intraoral accessory glands. *Surgery, Gynecology and Obstetrics*, **108:** 450–456.

Polymorphous Low-Grade Adenocarcinoma of Minor Salivary Glands

A Study of 14 Cases of a Distinctive Neoplasm

HARRY L. EVANS, MD, AND JOHN G. BATSAKIS, MD

M. D. Anderson Hospital cases diagnosed as adenocarcinoma of minor salivary glands before 1977 were reviewed. Within this heterogeneous group of neoplasms there was identified one clinicopathologic tumor entity, which we have designated "polymorphous low-grade adenocarcinoma." The 14 tumors in that category were characterized by cytologic uniformity and histologic diversity; growth patterns varied (both within and among cases) from solid to tubular to papillary to cribriform (pseudoadenoid cystic) to fascicular, while the cells were always small to medium-sized, regular, and lacking in nuclear atypia. Mitotic figures were infrequent, and tumor necrosis was seen in only one instance (a recurrent neoplasm). Clear cytoplasm, oxyphilic and mucinous metaplasia, and intratubular calcification were sometimes present, and stromal mucinization and hyalinization were common. The tumors were always unencapsulated, and exhibited extension into surrounding tissues including bone. The 14 patients ranged in age from 27 to 76 years (median, 64 years). Eight were male and six were female; eight were white and six were black. The neoplasm was intraoral in all cases, involving the palate in 11, the buccal mucosa in two, and the posterior mandibular area in one. Local recurrence developed in one case, cervical lymph node metastasis in one, and both recurrence and cervical lymph node metastasis in two. The number of successive recurrences ranged up to three, and the interval to recurrence varied up to nine years (the interval to metastasis up to five years). Although radical surgical procedures were necessary for tumor control in some cases, no distant metastases occurred and all patients were clinically tumor-free at latest follow-up.

Cancer 53:935–942, 1984.

IN MOST REPORTS on salivary gland neoplasms, "adenocarcinoma" is used as a generic designation for those malignant gland- or duct-forming tumors that do not show the characteristic features of adenoid cystic carcinoma, acinic cell carcinoma, mucoepidermoid carcinoma, or malignant mixed tumor. Apart from the description of epimyoepithelial clear cell carcinoma,[1,2] little progress has been made in identifying meaningful neoplastic entities within the adenocarcinoma group. In hope of improving on this situation, we decided to review M. D. Anderson Hospital cases filed as adenocarcinoma of salivary glands. Although our study of major gland cases was not fruitful in this regard, we did find within the minor gland neoplasms one true tumor type.

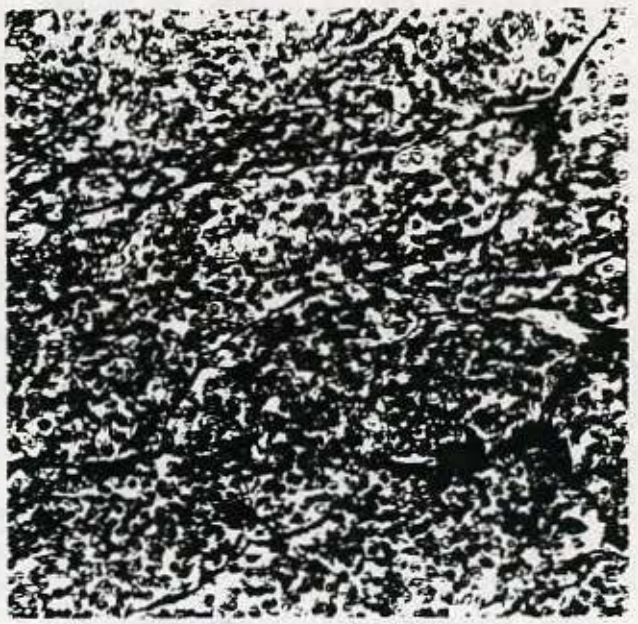

FIG. 1. Polymorphous low-grade adenocarcinoma: solid growth pattern. (All figures show polymorphous low grade adenocarcinoma.)

TABLE 1. Clinical Data on Patients with Polymorphous Low-Grade Adenocarcinoma

Case no	Age/sex/race	Tumor location	Tumor size	Initial treatment	Follow-up
1	68MB	Hard palate (midline)	2.5 cm	Excision, then 5000 rad	NET at 6 yrs
2	60FB	Buccal mucosa (left)	Unknown	Excisional biopsy, then 5000 rad + iridium implant	NET at 11 yrs
3	65FW	Hard palate (right)	2.4 cm	Excision	NET at 12 yrs
4	50MB	Hard palate (midline)	Unknown	Excision	Recurrence at 3 yrs: excision Second recurrence at 12 yrs involving palate, nasal walls and septum, and sinuses: resection of above structures Third recurrence at 19 yrs involving anterior maxilla: anterior maxillectomy NET at 20 yr
5	62MW	Junction of hard and soft palate (left)	3 cm	Excision	NET at 11 yrs
6	27MB	Buccal mucosa (right)	5 cm	Excision, then 6000 rad	NET at 6 yrs
7	63FW	Junction of hard and soft palate (midline)	2 cm	Biopsy, then 6500 rad + iridium implant to palate and 5000 rad to both sides of neck, then bilateral upper neck dissections (metastases in 2 lymph nodes from left neck, 1 from right neck)	Recurrence at 1 yr: excision NET at 7 yrs
8	36MB	Hard palate (right)	2.5 cm	Right partial maxillectomy including portion of palate and floor of nasal cavity and maxillary sinus	NET at 19 yr
9	69FW	Junction of hard and soft palate (left)	2 cm	Excision	Enlarged left cervical lymph nodes at 5 yr: left radical neck dissection (metastases in 4 nodes) Recurrence in left maxilla at 7 yrs: left partial maxillectomy Second recurrence in left maxilla at 16 yrs: left total maxillectomy and orbital exenteration NET at 18 yrs
10	76MW	Junction of hard and soft palate (midline)	Unknown	Excision	Enlarged left cervical lymph node at 2 yrs: left upper neck dissection (metastasis in 1 node) Died at 5 yrs of incidental cause, NET
11	50MW	Hard palate (left)	2 cm	Excision	NET at 18 yrs
12	73MB	Hard palate (left)	5 cm	Left partial maxillectomy, including resection of hard palate, nasal septum, and floor of nasal cavity, then 6000 rad	Died of incidental cause at 9 yrs, NET
13	60FW	Overlying posterior mandible (right)	2 cm	Right commando	NET at 19 yrs
14	67FW	Junction of hard and soft palate (right)	3 cm	Excision	Died of incidental cause at 6 yrs, NET

NET: No evidence of tumor.

Materials and Methods

M. D. Anderson Hospital cases filed as adenocarcinoma of minor salivary glands (including nasal glands) and diagnosed before 1977 were reviewed. This group of cases proved to be highly heterogeneous; however, within it there was identified one clinicopathologic tumor entity, which we have designated "polymorphous low-grade adenocarcinoma." The 14 cases included in the final study group were those in which our histopathologic criteria

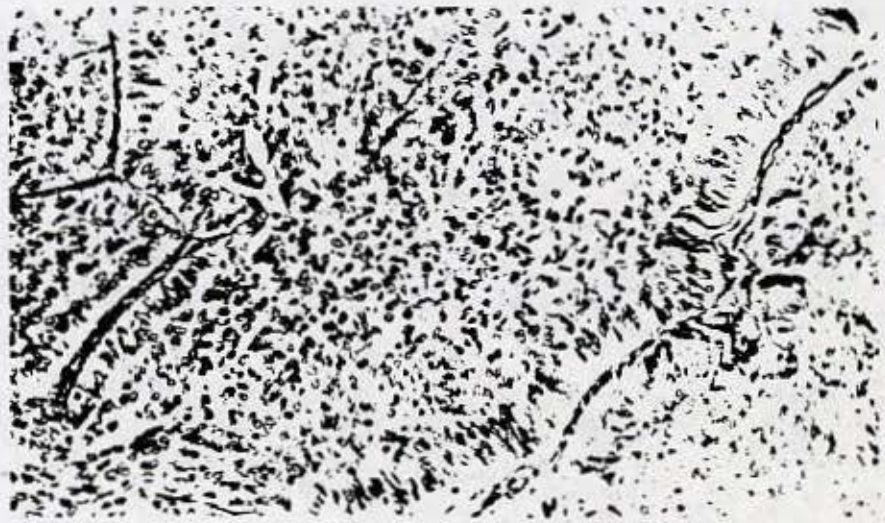

FIG. 2. At times, solid nests were bordered by columnar cells.

for this entity (to be detailed below) were satisfied and in which at least 5 years follow-up was available (follow-up was dated from the time of initial histologic diagnosis).

Results

Histopathologic Findings

The 14 tumors were characterized by cytologic uniformity and histologic diversity. The cells in all cases were small to medium-sized, regular, and lacking in nuclear atypia. Mitotic figures were few (less than 5 per 10 high-power fields). Tumor necrosis was seen in only one instance (the most recent recurrence in Case 4, Table 1) and was then only focal.

In contrast to this constant cellular blandness, there was considerable histologic variety, both from case to case and within individual cases. The spectrum of growth patterns included solid nests and trabeculae (Figs. 1–4), tubules (Figs. 4 and 5), papillae (Figs. 6 and 7), cysts (Fig. 7), cribriform or pseudoadenoid cystic formations (Fig. 8), strands (Fig. 9), and fascicles (Fig. 10). Combinations and transitions among these patterns were frequent.

In some cases there were areas in which the tumor cell cytoplasm was clear (Fig. 6) or, less commonly, oxyphilic (Fig. 11) or mucin-filled (Fig. 12). Intratubular calcification was an occasional finding (Fig. 13). The stroma within the tumors was often mucinous or hyalinized.

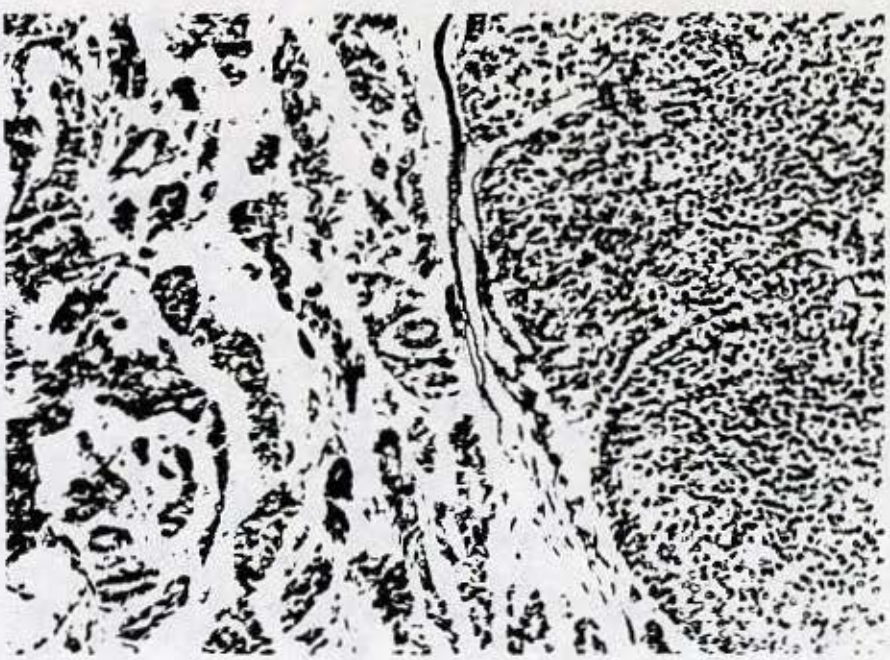

FIG. 3. Predominantly solid growth with large nest (right) and trabeculae (left). There are poorly formed lumens within some trabeculae (mucinous gland at bottom left is nonneoplastic).

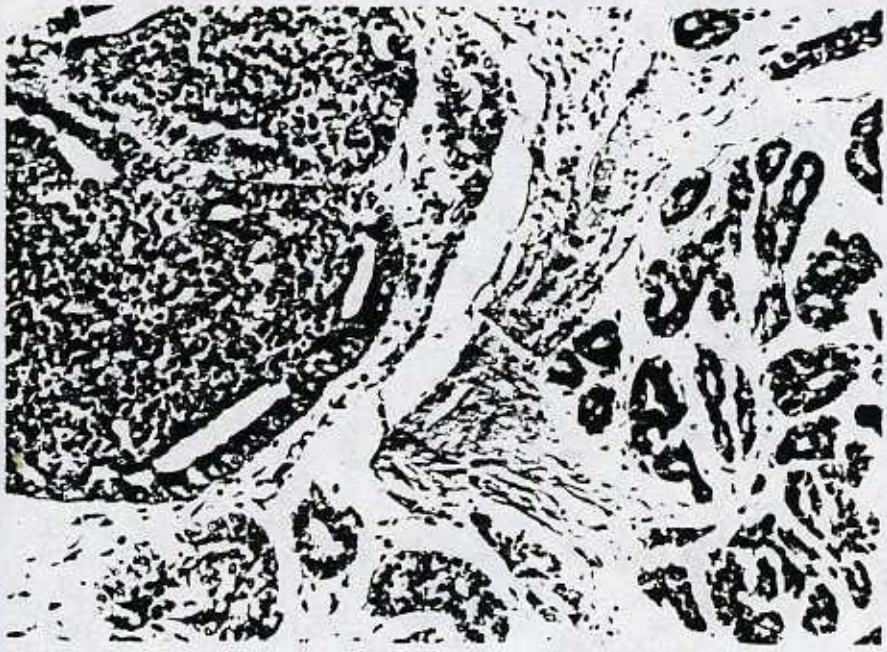

FIG. 4. Combination of solid and tubular patterns.

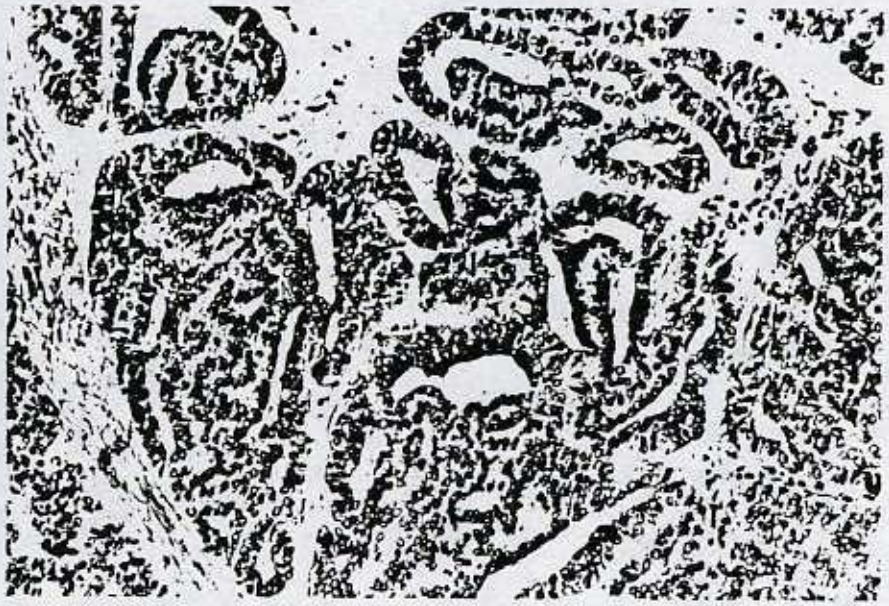

FIG. 5. Area with well-formed tubules.

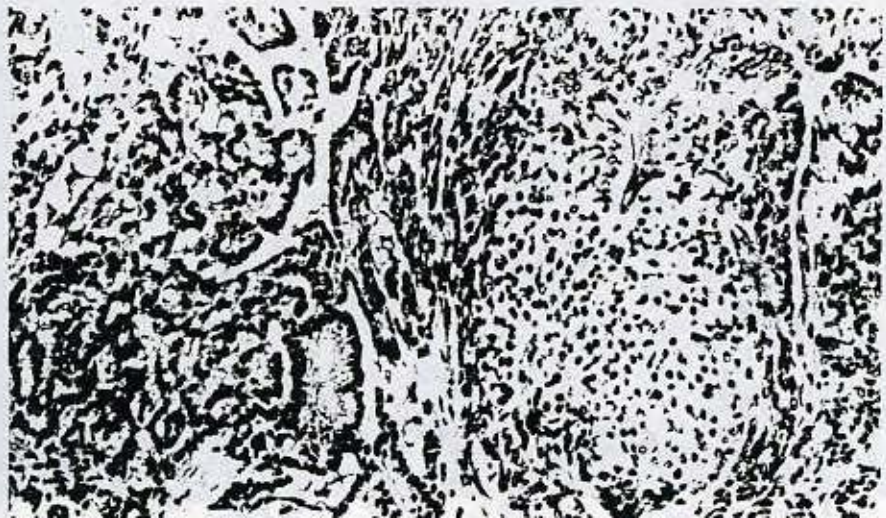

FIG. 6. Papillary structures at left; solid zone with clear cells at right.

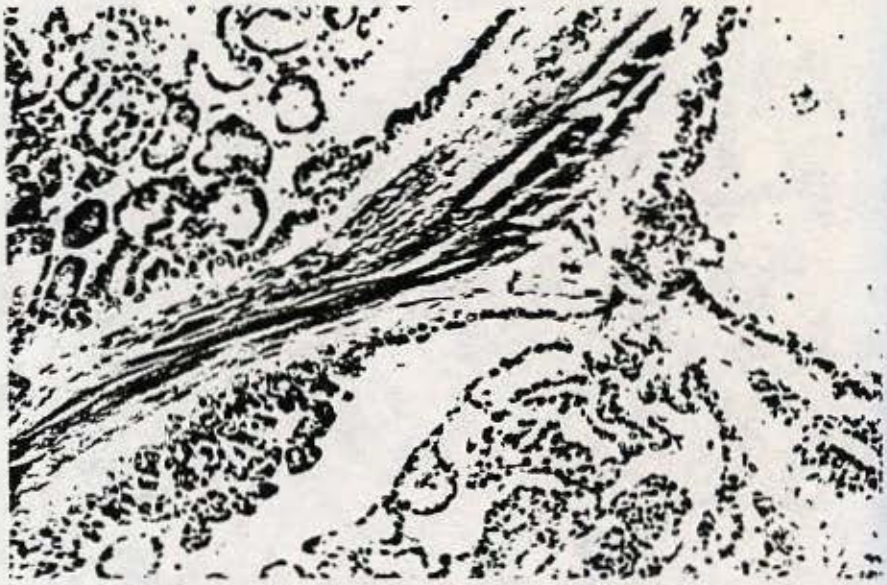

FIG. 7. Papillary-cystic pattern.

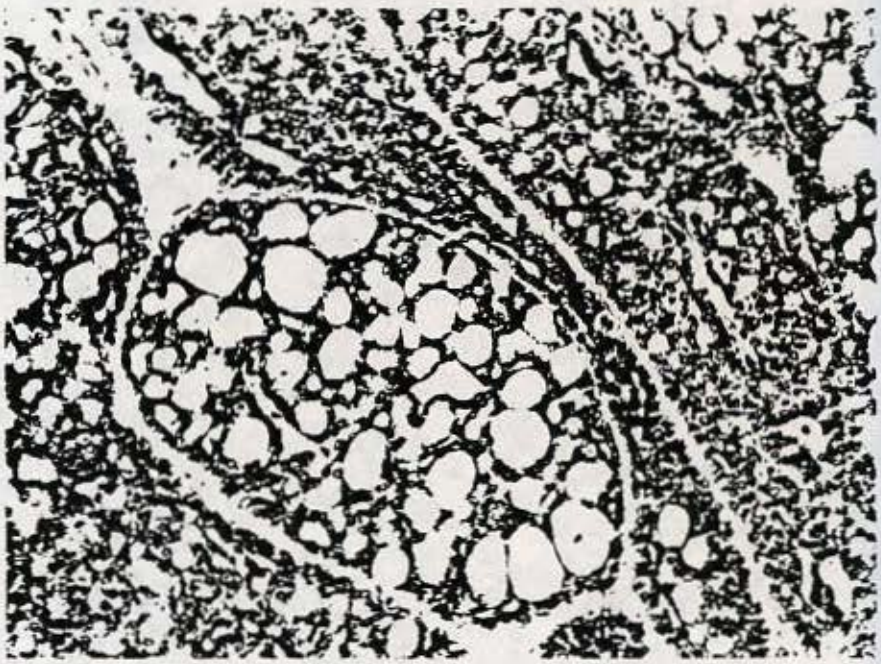

FIG. 8. Cribriform (pseudoadenoid cystic) pattern.

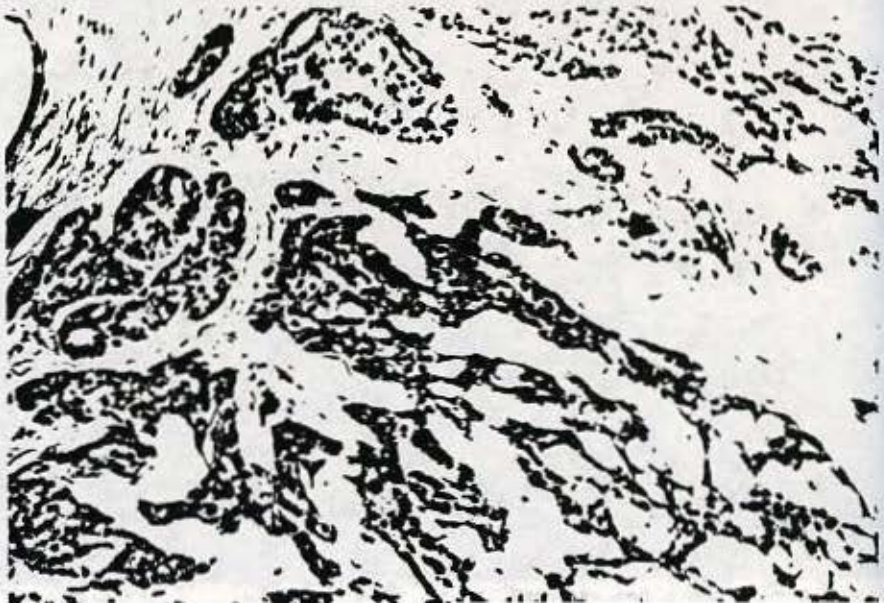

FIG. 9. Growth predominantly in anastomosing strands. Notice tubules at upper left.

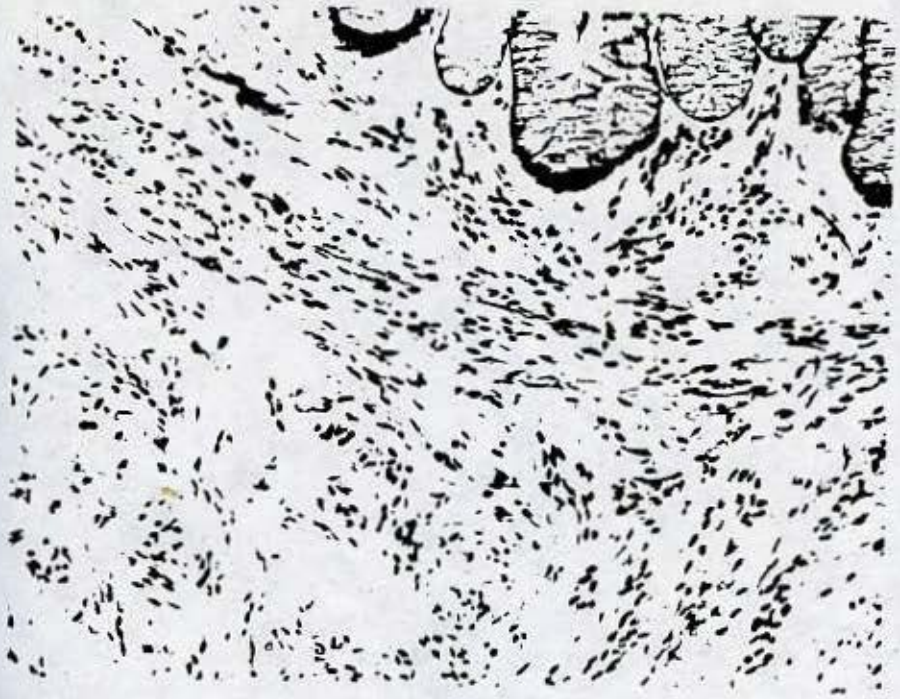

FIG. 10. Fascicular pattern with cellular elongation (mucinous glands are nonneoplastic).

All tumors were unencapsulated and exhibited infiltration into surrounding tissues (Fig. 14). Bone invasion was frequent when the neoplasm lay close to bone, and some palatal examples showed spread into the floor of the nasal structures (Cases 8 and 12, Table 1). Recurrent tumors often demonstrated more extensive involvement (Cases 4 and 9, Table 1). Perineural invasion was seen around small nerves in some specimens (Fig. 13) but was not significant clinically.

Age, Sex, and Race

The patients ranged in age from 27 to 76 years (median, 64 years) (Table 1). Eight were male and six were female; eight were white and six were black.

Tumor Location and Size

The tumor was intraoral in all cases; eleven were located on the palate, two on the buccal mucosa, and one in the posterior mandibular area (Table 1). Tumor size varied from 2 cm to 5 cm (median, 2.5 cm) in those cases in which information on size could be obtained.

Initial Treatment

Initial therapy is detailed in Table 1.

Follow-up

Table 1 gives follow-up information on each patient. Ten patients remained tumor-free after initial therapy.

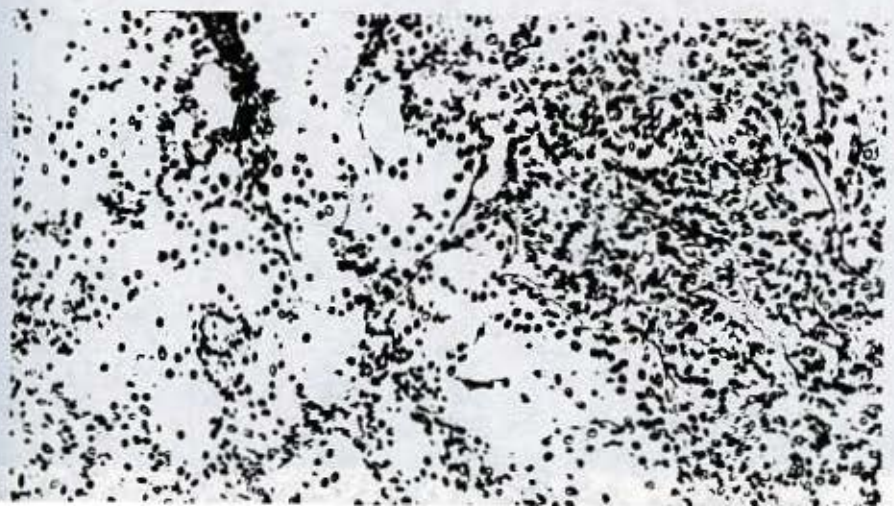

FIG. 11. Oxyphilic metaplasia.

One had local recurrence alone (Case 4), one had cervical lymph node metastasis alone (Case 10), and two had both recurrence and cervical lymph node metastasis (Cases 7 and 9). The number of successive recurrences ranged up to three (Case 4). The interval to first recurrence was 1, 3, and 7 years, respectively, in the three cases with recurrence (Cases 7, 4, and 9), while the interval between recurrences was as long as 9 years (Cases 4 and 9). Cervical lymph node metastasis was found at presentation in one patient (Case 7) and after intervals of 2 and 5 years, respectively, in the other two with metastasis (Cases 10 and 9). No metastases were observed elsewhere than cervical lymph nodes, and no deaths due to tumor occurred.

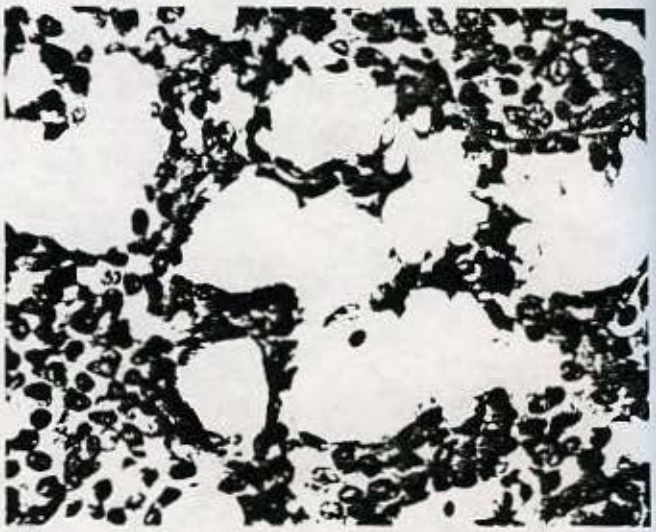

FIG. 12. Mucinous metaplasia.

Discussion

Although polymorphous low-grade adenocarcinoma has not been previously identified as a neoplastic entity, cases representative of portions of its histologic spectrum have been reported under other terms. In the study of Chaundhry *et al.*,[3] the tumors illustrated in Figures 12 and 14 and descriptively designated well-differentiated conventional adenocarcinoma and trabecular adenocarcinoma, respectively, are suggestive of polymorphous low-grade adenocarcinoma. Similarly, the series of intraoral adenocarcinomas presented by Stene and Koppang[4] contains several probable examples (which are not provided with specific nomenclature). The cases reported as papillary low-grade adenocarcinomas of the palate by Allen *et al.*[5] are almost certainly polymorphous low-grade adenocarcinomas with predominance of the papillary pattern, and those labeled papillary-cystic adenocarcinoma by Spiro *et al.*[6] may be as well (it is more difficult to judge in the latter instance because only one photomicrograph is provided). Recently, Batsakis *et al.*[7] assembled from current consultation cases a group of intraoral adenocarcinomas characterized by cytologic regularity and areas with fascicular growth (similar to Fig. 10 in this report) and designated these "terminal duct carcinoma." With the perspective of the current study, we now believe that these tumors (none of which are included here) are polymorphous low-grade adenocarcinomas with prominence of the fascicular pattern.

It would appear that polymorphous low-grade adenocarcinoma is at least primarily an oral neoplasm. In particular, it does not seem to be a significant consideration in the major salivary glands, judging from our survey of adenocarcinomas in that location.

We have chosen the term "polymorphous low-grade adenocarcinoma" in an effort to be clinically as well as morphologically descriptive. The behavior in our cases was that of indolent local aggressiveness with a potential for metastasis to cervical lymph nodes; although radical surgical procedures were required for tumor control in

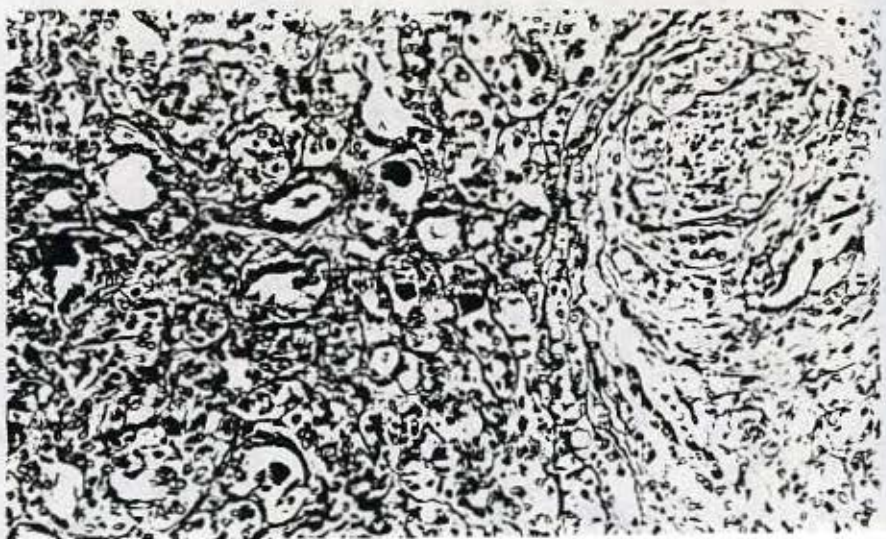

FIG. 13. Intratubular calcification. Notice perineural invasion at upper right.

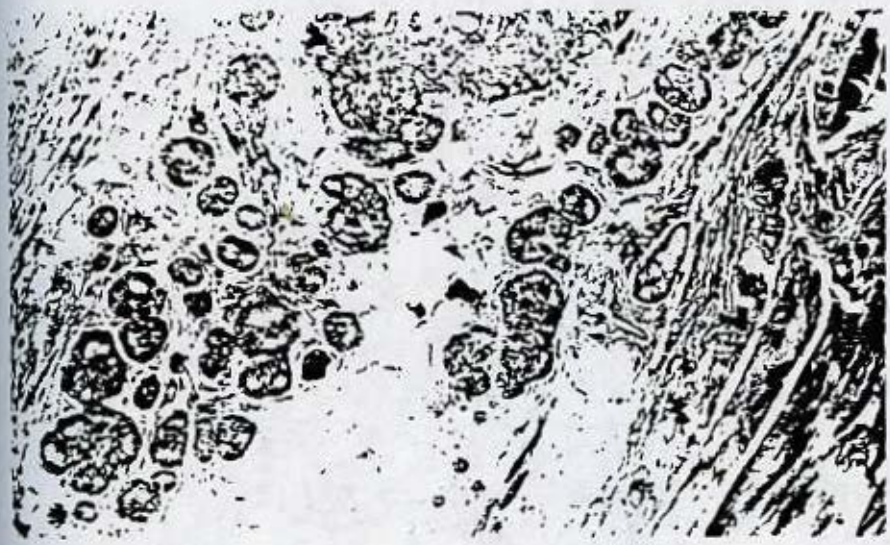

FIG. 14. Border of tumor, showing infiltrative growth and lack of encapsulation.

some instances, there were no distant metastases or deaths due to tumor. Even if both of the latter should occur on occasion, it is clear that the difference between the prognosis of polymorphous low-grade adenocarcinoma and the poor outlook usually ascribed to "adenocarcinoma" of salivary glands amply justifies recognition of this entity.

REFERENCES

1. Donath K, Seifert G, Schmitz R. Zur Diagnose und Ultrastruktur des tubularen Speichelgangcarcinoms: Epithelial-myoepitheliales Schaltstuckcarcinom. *Virchows Arch Pathol Anat* 1972; 356:16–31.

2. Corio RL, Sciubba JJ, Brannon RB, Batsakis JG. Epithelial-myoepithelial carcinoma of intercalated duct origin: A clinicopathologic and ultrastructural assessment of sixteen cases. *Oral Surg* 1982; 53:280–287.

3. Chaundhry AP, Vickers RA, Gorlin RJ. Intraoral minor salivary gland tumors: An analysis of 1414 cases. *Oral Surg* 1961; 14:1194–1225.

4. Stene T, Koppang HS. Intraoral adenocarcinomas. *J Oral Pathol* 1981; 10:216–225.

5. Allen MS, Fitz-Hugh GS, Marsh WL. Low-grade papillary adenocarcinoma of the palate. *Cancer* 1974; 33:153–158.

6. Spiro RH, Koss LG, Hajdu SI, Strong EW. Tumors of minor salivary origin: A clinicopathologic study of 492 cases. *Cancer* 1973; 31:117–129.

7. Batsakis JG, Pinkston GR, Luna MA, Byers RM, Sciubba JJ, Tillery GW. Adenocarcinomas of the oral cavity: A clinicopathologic study of terminal duct carcinomas. *J Laryngol Otol* 1983; 97:825–835.

Case 3. Monomorphic adenoma, oral cavity, buccal

Because of the several cytoarchitectural patterns assumed by monomorphic adenomas, the term is almost a contradiction of definition. Certainly, the older term, basal cell adenoma, is not a suitable one as a generic one for these tumors.

As may be derived from the accompanying reprints, there is considerable diversity in the monomorphic adenomas. The seminar case is just one form. The lobular architecture, amitotic cells and hamartomatous duct structures characterizes your case.

Monomorphic adenomas, unlike pleomorphic adenomas may be multifocal; approximately 10% in the major glands and higher in the oral cavity, especially in the labial-buccal mucosa.

There are malignant counterparts, so-called carcinomas ex monomorphic adenoma. Their behavior is not clear but probably is not unlike an adenoid cystic carcinoma.

A special group merits attention – the dermal analogue tumors – these lesions may be misdiagnosed as adenoid cystic carcinomas and may have a syndrome of salivary and cutaneous adenexal tumors.

Clin. Otolaryngol. 1981, 6, 129–143

Monomorphic adenomas of major salivary glands: a histologic study of 96 tumours*

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Monomorphic adenomas of major salivary glands: a histologic study of 96 tumours

It has been a little over a decade since monomorphic adenomas were formally recognized as a class of salivary gland tumours separable from the more common pleomorphic adenomas. This short time and a relatively low incidence, estimated at less than 2% of all salivary gland tumours, have not allowed histopathologic review of any sizable number of the tumours. The present study of 102 monomorphic adenomas; 96 in major salivary glands, establishes the histologic heterogeneity of the tumours and permits a classification based on this histologic variation as well as differences in histogenesis. For a number of the tumours, a hamartomatous deviation from stages in the normal organogenesis of salivary glands is strongly suggested. An analogous relationship exists for adenexae of the skin and their tumours. Identification of 12 tumours bearing a striking resemblence to dermal eccrine cylindromas carries the analogy further. Given the acceptance of the classification and time, a correlation of the subtypes of monomorphic adenoma with biological behaviour should follow.

Key words *monomorphic adenoma classification histogenesis dermal analogue tumours basaloid tumours*

The presence or absence of histologically definable stromal changes, e.g. myxoid, chondroid, in benign salivary gland tumours are used to separate *adenomas* of salivary tissues into two major histological classes—pleomorphic (mixed tumours) and monomorphic.[1] The qualifying terms are descriptive only and there should not be a histogenic implication by their use.

Monomorphic adenomas, as a class of salivary gland tumours, were formally proposed by Kleinsasser & Klein[1] who extracted them from their former inclusion with mixed tumours. Following the initial report, a surfeit of others (single cases or series) have appeared in the literature. In the event, the original, rather circumscribed clinicopathologic limits of the tumours have broadened and their taxonomic status blurred. After more than a decade of surgical—pathologic experience with 'monomorphic' adenomas, it would seem timely and appropriate to re-assess these tumours.

The present report, based on a histopathological study of 96 monomorphic adenomas of major salivary glands and 6 from minor salivary tissue serves as a departure for such a review. Since both classification of the tumours and the embryological development of salivary glands are integral to our study, these two aspects will precede the presentation of our observations.

* The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Air Force or Defense.

Classification

Histopathological classifications of disease are useful only if they serve one, or preferably all, of three purposes; 1 the classification is based on, or can provide, a frame-work for study of histogenesis; 2 the classification can provide tangible clinicopathologic correlates for selection of therapy; and 3 the classification affords transfer into the biological course of the disease or lesions. In the case of monomorphic adenomas, classifications have evolved into three related forms. The World Health Organization (WHO) classification distinguishes three types of monomorphic adenoma (cystadenolymphoma, oncocytoma, and 'other types').[2] The classification by Seifert & Schulz[3] expands this abbreviated form and is presented in Table 1. Our version, which will serve as the basis for this report, is shown in Table 2. Its underlying premise is that various architectural and cellular forms of some of the monomorphic adenomas reflect different stages in the organogenesis of salivary glands. In part, then, the classification is a histogenic as well as a histologic one, but it can serve as a beginning towards an understanding of biological activity. For an understanding of the histogenic implications, a brief summary of the development of salivary glands is warranted.

Table 1 Classification of monomorphic adenomas after Seifert & Schulz[3]

Cystadenolymphoma
Oncocytoma
Monomorphic adenoma (other types)
salivary duct
basal cell
clear cell
sebaceous lymphadenoma
mucous-producing adenoma

Table 2 Monomorphic adenomas: histogenic classification

A. Distal (terminal) duct origin
1. 'Basal cell' or basaloid adenoma
a solid
b trabecular-tubular
c canalicular
2. Membranous (replicated basal lamina) adenoma
a dermal analogue tumours
b others
3. Clear cell (non-mucinous) adenoma
4. Salivary duct adenoma
B. Distal and/or striated duct origin
1. Apocrine
a sebaceous lymphadenoma
b sebaceous adenoma
C. Striated duct origin
1. Cystadenolymphoma
2. Oncocytoma
D. Proximal duct origin
1. Mucinous adenoma
2. Epidermoid papillary adenoma

Histo- and morphogenesis of major salivary glands

With the exception of the lingual glands (including von Ebner's glands) and glands in the foregut-derived viscera of the head and neck (pharynx and larynx), it is *ectoderm* which provides the principal embryonic source for the epithelia of the major and so-called minor salivary tissues of the region.[4]

All of the glands arise from a proliferating epithelial anlage possessing intrinsic invasive properties. The anlage is surrounded by a basement membrane and also by a thin layer of oriented mesenchyme.[5] Whatever the definitive site of the gland, and with temporal developmental differences, the morphogenesis of the glands follows this sequence: 1 initial bud formation, 2 proliferation and elongation of cell cord (main duct primordium), 3 branching of the distal epithelial bulbs, 4 canalization of cell cords and terminal buds to form ducts and terminal tubules, and 5 morphologic and *functional* differentiation of ducts and secretory endpieces.[5] Embryogenesis and development of the epidermis and the cutaneous adenexae follow a similar progression.[6,7]

The processes which bring about the first four of these morphogenetic events are primarily epithelial proliferation, mesenchymal proliferation and condensation, and an *interaction* between these two elements. Mesenchymal-epithelial interplay is best manifested by the cleavage or indentation in the distal or terminal bulbs which signals the beginning of branching of the primordium.[5] Each branch, still a solid epithelial mass, terminates in end bulbs which

elongate, acquire a lumen and are transformed into terminal tubules.

Prior to lumen formation, the terminal bulbs consist of a peripheral basal layer of columnar cells surrounding a centre of more loosely arranged polyhedral cells.[4] After lumenization, terminal tubules consist of approximately 2 layers of cells with the inner cells containing a few secretion granules. Presumptive myoepithelial cells may be observed between the outer layer of cells and the basement membrane. Regarding the myoepithelial cells, it should be noted that their earliest sign of differentiation is coincident with the first evidence of any secretory activity in the fetal end-bud epithelia. The full complement and distribution of myoepithelium are achieved at the time the adult acinar-intercalated duct pattern is accomplished.[4,5]

The secretory endpiece of the intralobular parenchyma consists of the intercalated duct and acini and it is the last element of the anlage to achieve its adult phenotypic expression. It is also fairly well accepted that regeneration or replenishment of this distal unit is provided by 'reserve' cells of the intercalated ducts.[8]

Mention has already been made about the importance of the mesenchymal-epithelial interaction for development of normal salivary structure. The basal lamina also plays a key role. The lamina, produced by epithelium, contains supramolecular complexes of hyaluronic acid and proteoglycan which are arranged into an extracellular scaffolding that imposes structural form on the epithelium.[9,10] Components of the basal lamina are synthesized in substantially greater amounts at the surface of the distal ends of the growing and branching epithelium and tubules. Accumulation is also more prominent at sites along the salivary gland primordia showing the least amount of collagen.[9] The importance to structure of the basal lamina is clearly evident when one observes epithelia devoid of lamina placed in culture with mesenchyme. Lobular architecture of the epithelium is lost, reappearing only after elaboration of new lamina.[9]

Even though the basal lamina arises and appears to exercise an influence independent of the mesenchyme, the latter also possesses inductive influence and affects processes in changes of development of epithelial morphology. This is mediated by direct epithelial-mesenchymal and epithelial-neural contacts. Such contacts appear *after* the morphogenetic branching pattern of the glandular rudiment and *before* the onset of glandular secretion, differentiation of myoepithelial cells and maturation of specialized cells of the secretory endpieces.[5,9]

Materials and methods

The tumours included in this study were selected from the surgical pathology files of the Department of Oral Pathology, The Armed Forces Institute of Pathology, Washington, DC, and from the files of the consultation service of the senior author.

One hundred and two tumours were reviewed. Their numerical distribution, according to our classification, is given in Table 3 (p. 137). With the exception of 3 clear cell tumours and the 3 squamous papillomas, which originated in intra-oral minor salivary tissues, all of the tumours arose in either the parotid or submandibular glands. There were no mucous producing adenomas.

Cystadenolymphomas (Warthin's tumours) were not included in this study. This judgement was made because of the already extensive literature relating to this lesion. Also, except for their classification and enumeration, detailed analyses of clear cell tumours, oncocytomas, sebaceous lymphadenomas and epidermoid papillary adenomas were not done. In the case of the clear cell tumours, this omission is due to a concurrent study of those lesions at the Armed Forces Institute of Pathology. For the other three types of tumours, either an ample existing documentation or a minor salivary gland predilection served as the basis for exclusion.

The age of the 82 remaining patients at the time of the clinical presentation of their monomorphic adenomas ranged from 1 day (neonate) to 74 years. Only 20 patients were younger than 50 years-of-age. There was a 5:1 male predominance.

Haematoxylin and eosin stained tissue sections were available from each of the 102 tumours. Where indicated and available, addi-

tional histologic preparations were prepared from submitted formalin-fixed tissues. An average of five sections from each tumour were studied. Special staining procedures used were; PAS for demonstration of basal lamina, trichrome stains for stoma, and mucicarmine and/or alcian blue for mucin.

Results of light-microscopic study

BASALOID ADENOMAS

These tumours were the most frequent type of monomorphic adenoma in this study. They presented in 3 basic histologic forms; trabecular-tubular, solid, and canalicular. Except for the canalicular type, the growth patterns in a given basaloid adenoma were sometimes intermingled, but a dominant architecture prevailed, thus allowing subclassification.

Canalicular basaloid adenomas were the least common (4 cases) and all were parotid tumours. An apparent encapsulation was present in all 4 tumours. Distinctive in histologic appearance, the tumours were composed of columns, tubes and abortive glandular spaces with cuboidal or columnar epithelial cells (Figure 1). Stroma was always sparse, acellular, and proteinaceous. Both their appearance and relative frequency in major salivary glands are in accord with an earlier AFIP study which indicated a marked proclivity for oral sites, especially the lips.[11]

Sixteen of the basaloid adenomas were classified as *solid* types. This form of monomorphic adenoma is the one most closely resembling the early, pretubular stages of embryonic development of salivary glands. As such, a stromal component is not conspicuous (Figures 2 & 3). The epithelial masses in all cases were delimited by a thin, regular basal lamina. In isolated fields, in a few tumours, replication of the basal lamina was found. Ductal or tubular components were few in number in any tumour and usually not well developed. A capsule, complete or partial, was present in 12 of the 16 tumours. All of the solid adenomas occurred in the parotid gland and when position of the tumour could be ascertained, they were superficially located in the lateral lobe.

Trabecular-tubular adenomas were the most common of the basaloid adenomas. Two of the 34 tumours involved the submandibular gland; the remainder were parotid gland in origin. One of the submandibular tumours presented in a neonate with surgical removal performed at 2 months of age because of increasing size of the tumour. In general, these basaloid adenomas manifested the most 'orderly' growth pattern of the group. They also displayed the most conspicuous interepithelial stroma (epithelial: stromal ratio of 80:20). The stroma, however, never manifested any of the characteristics found with pleomorphic adenomas.

Where the trabeculae had lumens, the appearance was that of tubular differentiation from the solid trabeculae. In only the neonatal tumour was there significant evidence of secretory endpiece differentiation from such tubules (Figure 4). Cellular alignment about the tubules was usually uniform and consisted of a double layer of epithelium with two distinct cell types; both confined by a thin basal lamina (Figure 5).

Paradoxically, despite the over-all orderliness of the anastomosing trabeculae, this form of basaloid adenoma was the one which manifested the greatest incidence of an admixed solid pattern.

Encapsulation, to varying degrees was present in 32 of 34 cases. While there appeared to be a tendency for a peripheral location, these tumours were just as likely to be found within the deeper parenchyma of the involved glands.

MEMBRANOUS ADENOMAS

These monomorphic adenomas are characterized by an excess production of an eosinophilic basal laminar material which presented in the following distributions: a separating epithelial masses from stroma, b hyaline cuffs around blood vessels within the tumours, c small droplets amongst epithelial cells, and d larger, coalescent masses entrapping and crowding epithelial cells (Figures 6 & 7).

Of all of the monomorphic adenomas, membranous adenomas conveyed the least orderly appearance. This is due to several factors. None of the tumours were monolobular and only 6 of the 12 were encapsulated. Five of the tumours were deemed to arise from multiple foci. As a consequence, an invasive quality was imparted

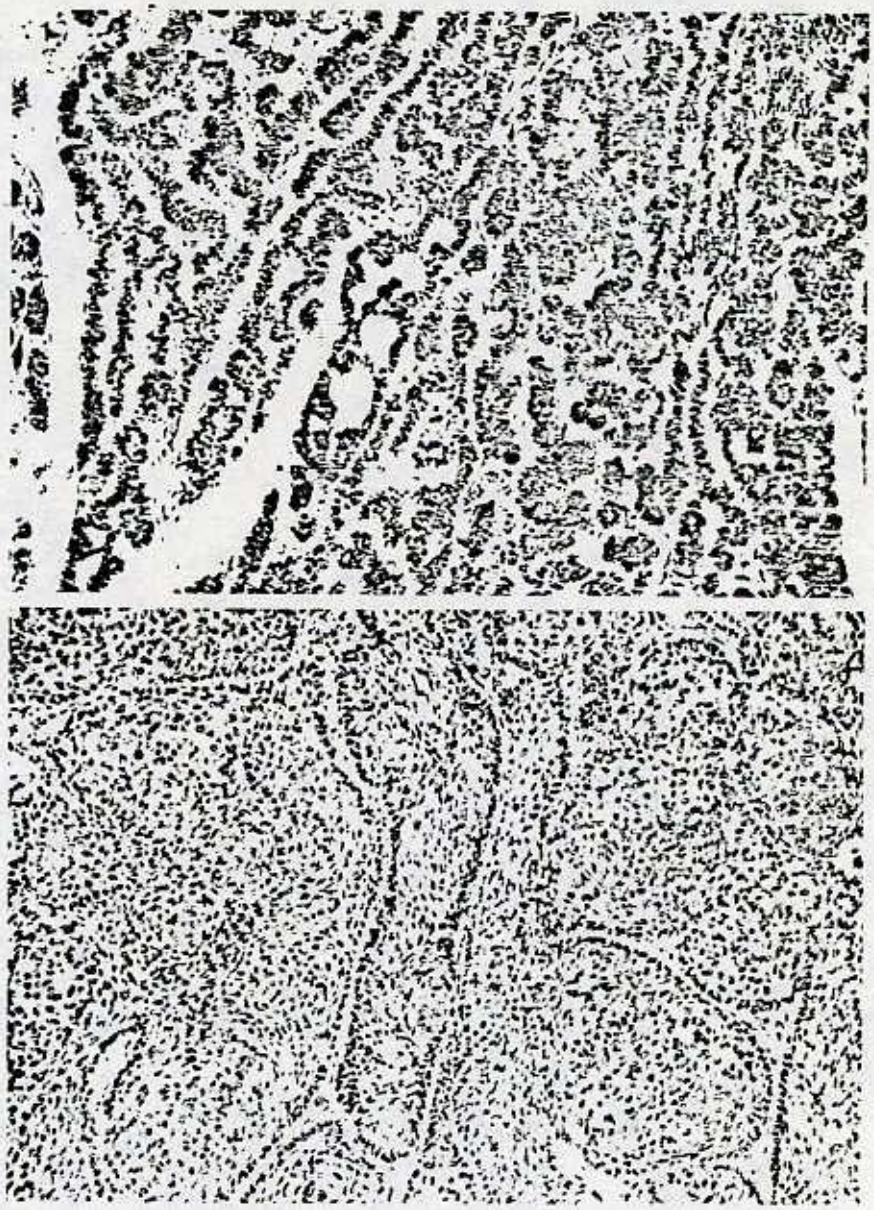

Figure 1 Canalicular form of basaloid monomorphic adenoma. Ribbons and cords of small dark cells with scant intercellular stroma. The site of origin of this form is usually in oral salivary tissues. H & E. × 133.

Figure 2 Solid basaloid adenoma composed of cellular epithelial masses surrounded by a thin basement membrane. Note the peripheral palisading of cells. H & E. × 98.

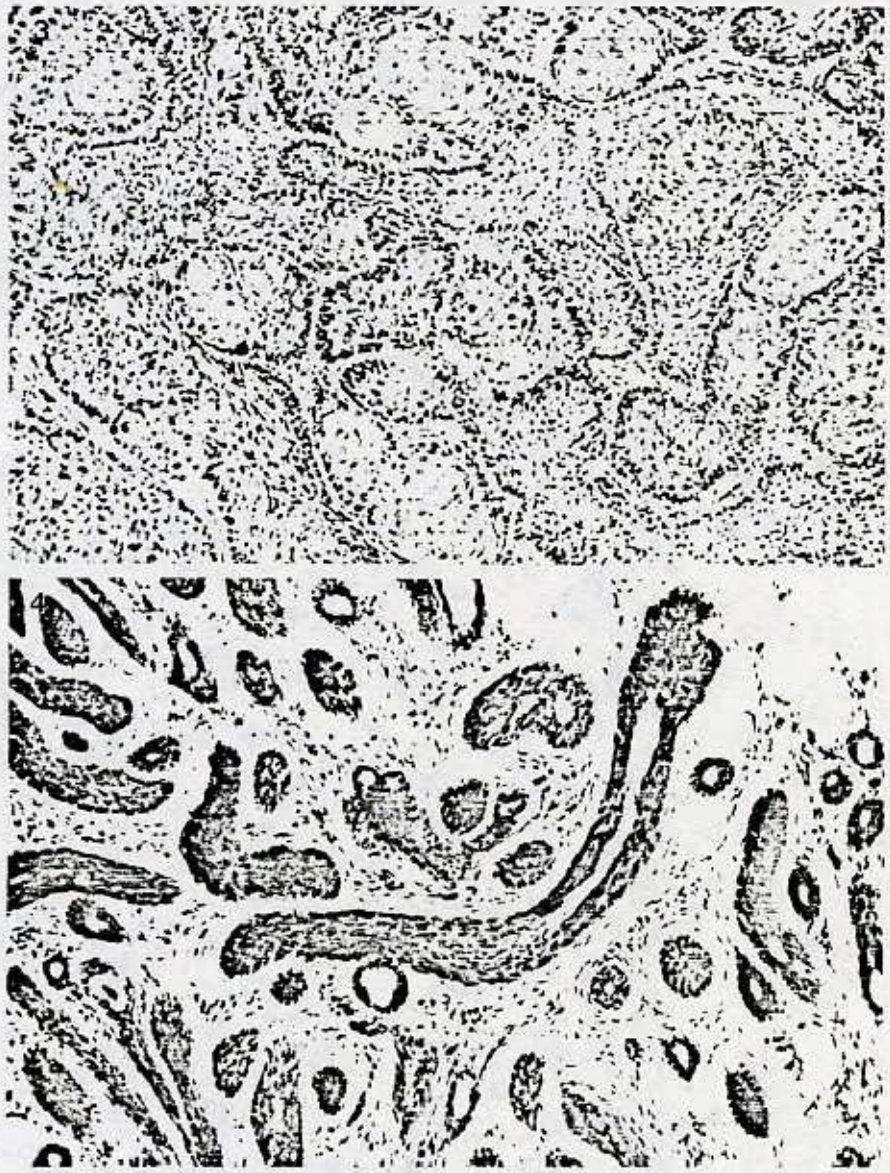

Figure 3 Solid basaloid adenoma nearly histologically identical to the tumour shown in Figure 2. It is this type of monomorphic adenoma which corresponds most closely to the pre-canalized epithelial buds of the embryonic salivary gland. H & E. ×98.

Figure 4 Submandibular gland tumour present at birth and excised from the patient at 2 months-of-age. A distinct hamartoma-like picture is conveyed by the trabecular-tubular architecture and early, but minimal secretory end-piece differentiation. Note too the poorly developed interepithelial stroma and occasional thickened basement membrane. The abortive functional differentiation and canalization, in company with the stroma, is highly suggestive of a failure of mesenchymal-epithelial interaction leading to abnormal development. H & E. ×120.

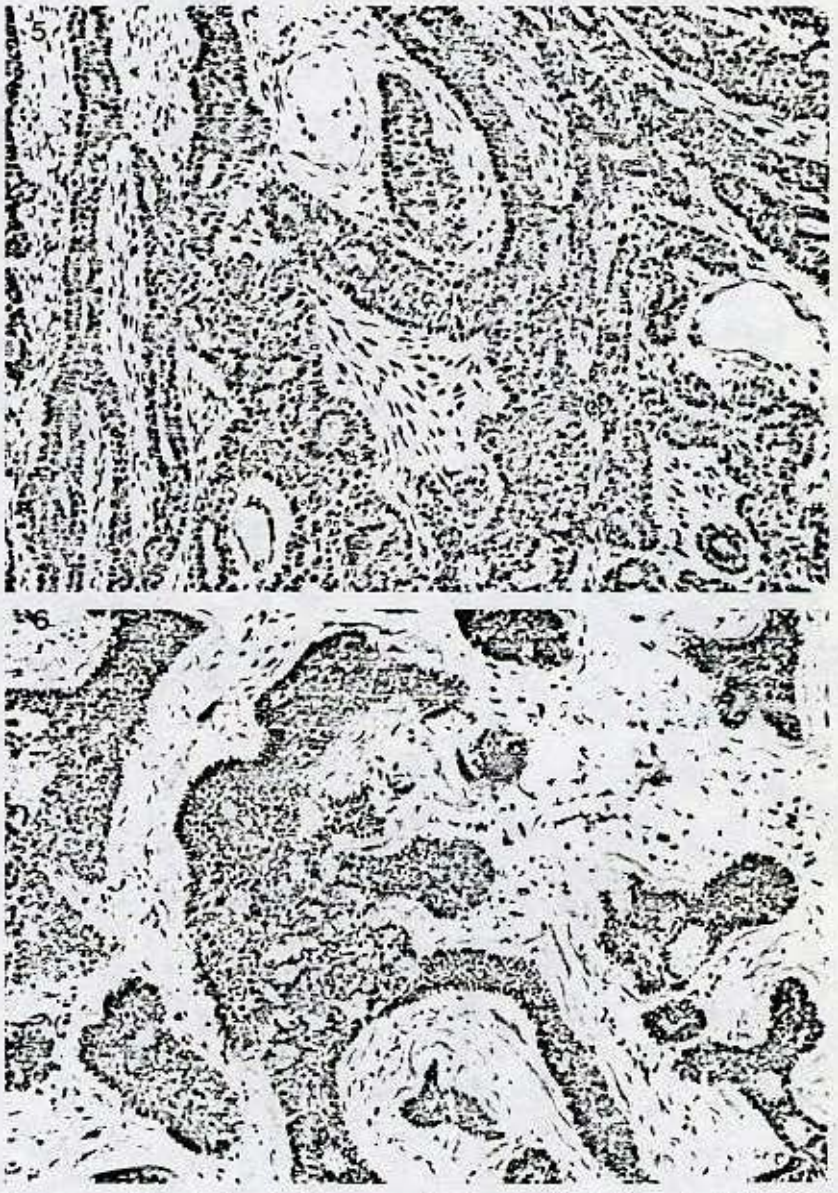

Figure 5 Typical microscopic appearance of a trabecular-tubular monomorphic adenoma. A double-layered epithelium is evident, as are the vascular and stromal characteristics of these tumours. H & E. ×112.

Figure 6 Membranous adenoma of dermal analogue type from parotid gland. Histological similarity to the dermal eccrine cylindroma is evident. The thickened basement membrane (replicated lamina) suggests abberation of the scaffolding for normal salivary lobule development. This tumour was removed from a patient with cutaneous dermal tumours of eccrine type. H & E. ×105.

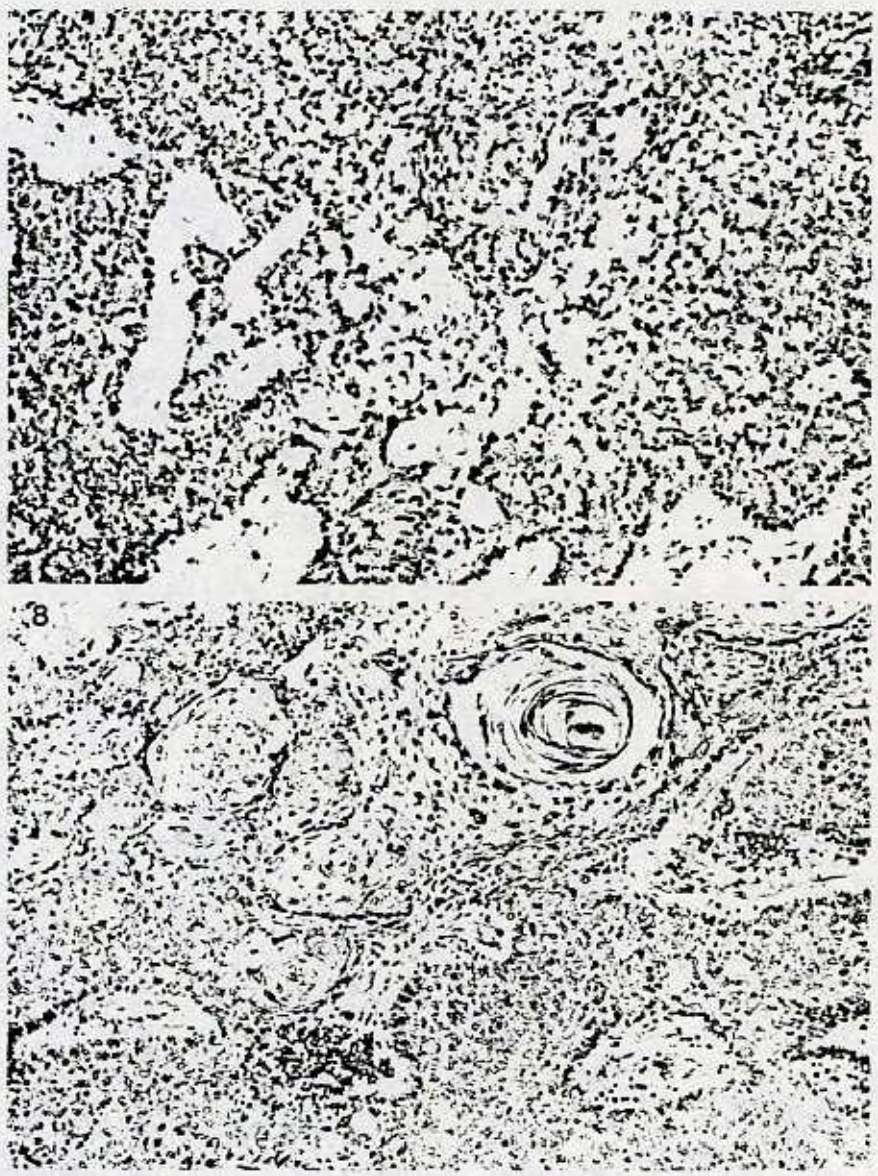

Figure 7 Membranous adenoma of dermal analogue type exhibiting irregularly deposited and increased amounts of basement membrane material. H & E. × 140.

Figure 8 Epidermoid and sebaceous cell differentiation in a membranous adenoma of parotid gland. H & E. ×126.

to this group with lobular and cellular extensions or an appearance of a disrupted jig-saw puzzle separated by stroma.

Because of the marked resemblance to the dermal eccrine cylindroma, we have subclassified all of our membranous adenomas as dermal analogue tumours. At least 2 cells participate in the formation of the tumours; small 'basal' cells with scant cytoplasm and deeply chromatic nuclei and less numerous, larger, polyhedral cells with paler nuclei. The latter often assumed a whorled pattern, not unlike similar cells in the solid basaloid adenomas and like them also manifested epidermoid features. Indeed, in foci, there was an abrupt true squamous change and keratinization in such cells (Figure 8). Sebaceous cell differentiation, never prominent, also was present in some tumours.

The small, dark cells had the more intimate relation to the basal laminar material and where the two cells coexisted, the smaller cells were peripherally located.

Ten of the dermal analogue tumours presented in the parotid gland; 2 in the submandibular gland. In the parotid gland, the tumours were superficial in the lateral lobe. Three gave microscopic evidence of origin and confinement within peri—or intraparotid lymph nodes. Except for the tumours whose origin was considered to be intra-nodal, a capsular confinement was either not present or scant.

The analogous relationship to dermal tumours, especially the dermal eccrine cylindroma was heightened by the findings in three patients of synchronous or metachronous salivary gland and cutaneous tumours of similar histological types. In each patient, the salivary gland tumours were dermal eccrine analogues and the skin lesions were eccrine cylindromas, trichoepitheliomas and eccrine spiradenomas. No other monomorphic adenoma exhibited such an association.

SALIVARY DUCT ADENOMAS

This designation does not include the adenomas of the excretory duct and they are histologically separable from the trabecular-tubular adenomas by being composed entirely of closely apposed well-formed small ducts without a lumenless trabecular component. The ducts appear to be intercalated in type and are uni- or double layered (Figures 9 & 10). Four of the 16 tumours lacked any degree of encapsulation and 2 were multifocal in the same parotid gland. All were parotid lesions. All 4 of the unencapsulated tumours were less than 0.5 cm in major dimension.

Discussion

Mistranslation of the adjective 'monomorphic', to indicate 'unicellular' is just one of the factors responsible for uncertainty over the cellular derivation and composition of monomorphic adenomas. As to derivation, it is clear that a single histogenic hypothesis cannot be successfully applied to all forms of the monomorphic adenomas listed in Table 3. Assertions that myoepithelial cells are not found in monomorphic adenomas remain unproven. Even with light microscopic evaluation, a heterogeneity of the cell population of some of the monomorphic adenomas is evident. Heterogeneity is also underscored by enzyme histochemical studies which indicate cells and mucosubstances of differing histochemical properties, comparable to those of myoepithelial cells and ductal cells of adjacent salivary tissues.[12] A similar diversity of cells has been found by some electron microscopists.[13]

Distinction between a hamartomatous state and neoplasia is never readily accomplished.

Table 3 Histological classification of 102 monomorphic adenomas

Histological type	*No. of cases*
Basaloid adenomas	
trabecular-tubular	34
solid	16
canalicular	4
Dermal analogue tumours	12
Salivary duct adenomas	16
Clear cell tumours	5*
Oncocytomas	6
Sebaceous lymphadenomas	6
Epidermoid papillary adenomas	3†
Total no. of cases	102

*3 in minor salivary glands.
†Minor salivary glands.

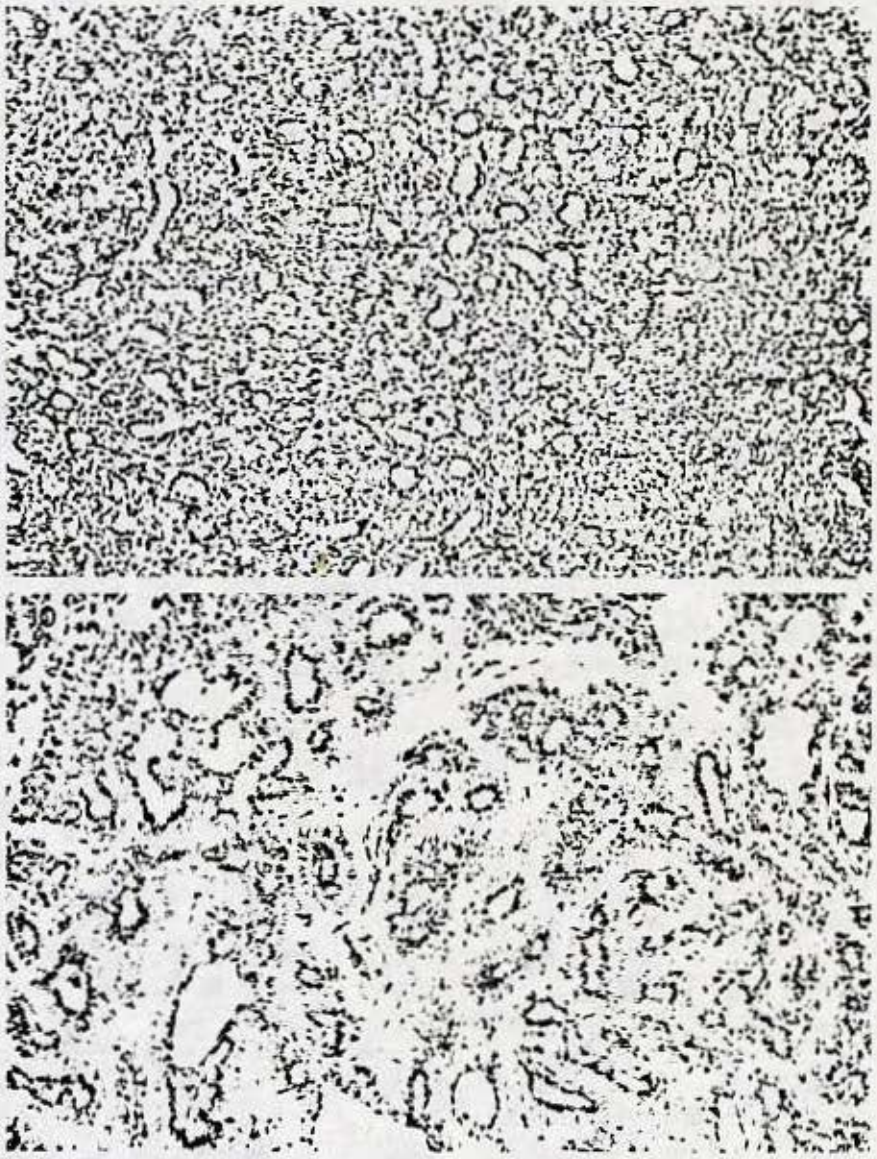

Figure 9 Salivary duct adenoma. This monomorphic adenoma is characterized by variably differentiated ducts; usually closely apposed and without the histological features in the stroma which are associated with pleomorphic adenomas. H & E. ×70.

Figure 10 Salivary duct adenoma. In this variant, the duct lumens have a double epithelial lining. H & E. ×98.

Indeed, it is difficult or impossible to say when progressive enlargement of a hamartoma ends and neoplasia begins. In that light, *adenoma* may be an inappropriate designation for the non-mucinous clear cell tumour since they often manifest a biological behaviour of malignancy.[14,15]

The foregoing uncertainties aside, however, certain objective and subjective findings from study of the present series allow for a more circumspect, if not precise, analysis of monomorphic adenomas of salivary tissues.

The putative cells of origin of monomorphic adenomas are the salivary duct cells or their reserves.[4,8] As shown in Table 2, all 3 segments of the salivary duct unit participate. The least differentiated, in the sense of post-embryonic morphogenesis, are the derivatives from the

distal part of the salivary duct unit, i.e. intercalated ducts. Since intercalated duct cells are believed to be a reservoir for distal striated ductal epithelium, one can find them or their precursors in some of the monomorphic adenomas whose origin is principally from striated ducts, e.g. cystadenolymphomas and sebaceous lymphadenoma.[4] Mucinous and epidermoid papillary adenomas appear to originate solely from the excretory ducts.

Should the myoepithelia play a role in the formation of monomorphic adenomas, as suggested in some clear cell tumours, their contribution is limited to those tumours originating from the intercalated duct and possibly the distal striated duct. Their normal absence in more proximal parts of the salivary duct unit would preclude a presence in tumours arising from these parts.[4,8]

Many of the monomorphic adenomas arising from the terminal or distal ducts histologically qualify as hamartomas in that their appearance is either analogous to stages of the embryonic development of normal salivary glands or are disordered caricatures of the development. A delayed (chronologic) appearance of the tumour does not obviate such an observation. It is further pertinent to our discussion that a similar analogy is proposed for the histogenesis of cutaneous basal cell epitheliomas and adenexal tumours.[6] Clinico-pathological linkage between tumours of the skin's basal germinative layers and monomorphic adenomas of the terminal duct system is provided by the existence of a salivary gland—skin tumour diathesis, possibly representing an effect of a pleiotropic gene acting on ontogenetically related stem cells. Three of our patients exhibited this diathesis and additional cases have been presented by Headington *et al.*[16] and Reingold *et al.*[17] The salivary gland tumours have been analogues of dermal cylindromas and the synchronous or metachromous adenexal tumours have been dermal cylindromas, eccrine spiradenomas and trichoepitheliomas. Analogous monomorphic tumours have also occurred in the breasts of dogs and humans.[18,19]

On the basis of embryological studies and in-vitro manipulations of salivary gland primordia, it is likely that the varied cytoarchitectural pattern presented by many of the monomorphic adenomas (particularly the basaloid and membranous types) result from defects or aberrations in epithelial—mesenchymal interactions and/or formation of basal lamina.[5,9] The neonatal tumour of the submandibular gland in this series likely represents a maldevelopment of a major portion of that gland's organogenesis wherein canalized epithelial cords exhibit focal areas of secretory endpiece differentiation. The solid forms of basaloid adenoma lack any significant duct formation and intercellular stroma, but have a defined, uniform basement membrane; recapitulating the precleavage, cytodifferentiation stage of salivary gland development. Other patterns reflect hamartomatous deviation from later stages of embryological development, again with a uniform basement membrane.

Haphazard and excessive basal laminar material typifies the dermal cylindroma analogue tumours of salivary glands. And while there is no normal embryonic equivalent, the observed multifocal character of these tumours and the irregular islands of epithelium and their coalescence points to a mishapen scaffolding (basal lamina) as an underlying cause. Aberrant cytodifferentiation in the form of squamous cells and small, indifferent cells further indicates a lack of an organizing influence.

Many monomorphic adenomas exhibit a noteworthy peripheral or superficial location in the major salivary glands; particularly in the parotid gland. For some of the tumours, such as the cystadenolymphoma, a peripheral location is attributable to origin from ductal elements included within lymph nodes (intra- or periparotid). Sebaceous lymphadenomas also often evince a peripheral or apparently juxtaparotid position and this coupled with their characteristic lymphoid stroma point to a form of histogenesis which is congeneric with the cystadenolymphoma's.[20] That sebaceous elements are more frequently associated with cystadenolymphomas than with any other salivary gland tumour offers indirect support.

Intranodal, extra-salivary locations for monomorphic adenomas are not limited to the 2 aforementioned adenomas. Three of the dermal cylindroma type tumours exhibited this feature.

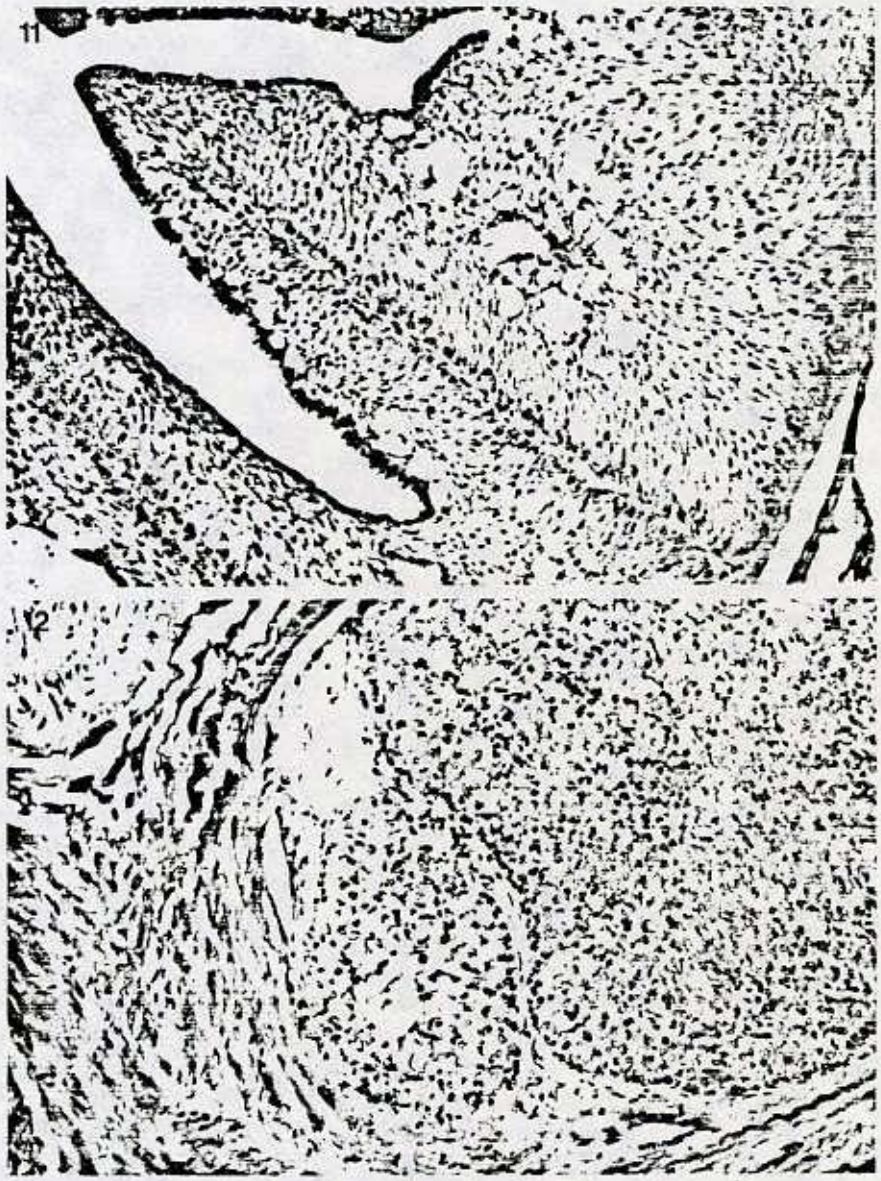

Figure 11 Monomorphic adenoma of squamous or epidermoid type. The epidermoid papilloma often has a columnar epithelial surface surmounting the epidermoid cells. In this study, this tumour was exclusively an oral or lip lesion. H & E. × 140.

Figure 12 Dermal analogue monomorphic adenoma encroaching on a small nerve bundle of the VII nerve. A similar association with nerves is also seen in the dermal equivalents (dermal eccrine cylindroma) and does not represent invasion. H & E. × 140.

Mucinous adenomas and papillary epidermoid adenomas (Figure 11) are not pathogenetically related to the other monomorphic adenomas; either by cell of origin or by histological phenotype. Their extralobular and unifocal intraductal location indicates an excretory duct origin.[21]

Monomorphic adenomas whose epithelial components are oncocytes are also not pathogenetically related to the other classified adenomas. Their derivation is from modified or transformed existing ductal cells which are responding in an oncocytic fashion to intracellular changes in metabolism.[22]

The biological course of monomorphic adenomas, in aggregate, has been considered to be one of a benign, usually non-recurrent lesion.[1,3] Such behaviour may reflect the hamartomatous nature of some of the tumours, but is more likely a result of clean extirpative surgical removal; a relationship shared by pleomorphic adenomas. Persistence of tumour nevertheless occurs and adequacy of excision aside, is fostered by the multinodular and more importantly, multifocal origin of several of the subtypes of monomorphic adenomas, i.e. cystadenolymphomas, some salivary duct adenomas and dermal analogue tumours. For the latter type, multifocality represents yet another correlation with basal cell epitheliomas and adenexal tumours of skin. It further distinguishes them from pleomorphic adenomas where demonstrated multifocal origin is of a very low order—0.5% or less.[23]

An accurate assessment of the frequency of recurrence/persistence of various types of monomorphic adenoma is not possible, nor should such statistics be interpreted as being intrinsic to the tumour's proliferative ability. Table 4 presents the observed recurrence rate in 4 series of cystadenolymphomas.[24–27] In our small group of dermal analogue salivary gland tumours, the recurrence rate (25%) is higher and correlates well with the observed recurrence rate for their dermal counterparts (42%).[28]

Projections of biological course should also consider potential histopathologic and clinical evolution were the adenomas not removed. Any basis for such reasoning is admittedly subjective or inferred by the occurrence of so-called hybrid forms (co-existence and merger of another benign or malignant lesion with the monomorphic adenoma).

Table 4 Cystadenolymphoma: 'recurrence rate'

Series	*No. of tumours*	*No. of recurrences (%)*
Foote & Frazell[24]	50	6 (12)
Eneroth[25]	15	1 (6)
Potdar[26]	12	1 (8)
Döbrössy *et al.*[27]	17	2 (12)

The first assumption to be tested is that some monomorphic adenomas are merely stages in the development of a pleomorphic adenoma. The only monomorphic adenomas where this is likely are the salivary duct adenomas and some basaloid adenomas. All of the other types have sufficient histopathologic uniqueness and singularity that a transition to pleomorphic adenoma is difficult to reconcile.

At this time, acceptance of the hypothesis that some monomorphic adenomas, given biological and chronological time, will evolve into pleomorphic adenomas, is not possible. Resolution must await a more definitive role of the myoepithelial cells in the formation of pleomorphic adenomas and also whether such cells participate in monomorphic adenomas. Such a stance does not deny the presence within pleomorphic adenomas of foci entirely consistent with those comprising some monomorphic adenomas.

Identification of malignant change in a monomorphic adenoma is more objective, at least from a histopathological point of view. Criteria to be used are those for a diagnosis of carcinoma ex pleomorphic adenoma; histopathologically definable carcinoma arising in a still recognizable maternal benign tumour. The recorded frequency of such a change in any of the monomorphic adenomas, with the exception of the clear cell tumours is much lower than the incidence of carcinoma ex pleomorphic adenoma.

Epithelial malignancy in a cystadenolymphoma exists in 3 forms. The most common is a co-existent, separate neoplasm. A metastasis to the lymphoid component of the cystadenolymphoma follows and the least common is a primary carcinoma arising from the ductal components of the tumour. Most of the latter, reported in the literature, are flawed cases and cannot withstand close scrutiny. Seifert *et al.*[29] found only 1 carcinoma arising in a cystadenolymphoma in their own series and Batsakis has estimated the event to occur in only 0.3% of all Warthin's tumours.[30] Three histological types of carcinoma may be found; squamous cell, undifferentiated and adenocarcinoma. Squamous cell carcinomas arise from metaplastic epithelium. Because of their rarity, only an esti-

mation of the clinical malignancy of these neoplasms is possible. Six of the 7 cases reviewed by Seifert *et al.*[29] had metastases to regional lymph nodes and one of the 6 also manifested distant metastases.

Prediction of the malignant potential of oncocytomas based on study of their *cytomorphology* by either light or electron-optic microscopy is not reliable.[22] Similar difficulties have been voiced by others studying related tumours in the thyroid gland, lungs, and kidneys. It is tempting to suggest a high degree of mitochondrial hyperplasia and pleomorphism is related to malignancy, but this has not been shown to be true. The only reliable histopathological indicators are the traditional ones; local destructive infiltrative growth, perineurial, lymphatic or vascular invasion and confirmed metastases. With these criteria, there are less than a dozen acceptable cases of oncocytic carcinoma. Their behaviour is not unlike adenocarcinomas of salivary glands, i.e. metastases to regional lymph nodes and distant sites. It is our contention that oncocytic transformation, *per se*, does not ameliorate or accelerate biologic malignancy of the carcinoma.

Carcinoma arising in sebaceous monomorphic adenomas rather than *ab initio* from non-adenomatous sebaceous elements in salivary glands is not only rare, it is difficult to prove.[31] Excluded from consideration are those cases in which malignant sebaceous components are found in carcinomas ex pleomorphic adenoma, mucoepidermoid carcinomas and other classes of primary epithelial malignancy of the glands. Furthermore, before ascribing a salivary gland origin to a sebaceous malignancy, it is pertinent to recall that the skin of the head and neck is the area with the highest incidence of sebaceous cell tumours in the body. Deep infiltration from a periparotid primary sebaceous carcinoma may obscure origin of the neoplasm.[31]

The 11 cases of 'primary' sebaceous cell carcinoma of the parotid gland accepted by MacFarlane *et al.*[32] contained only one acceptable origin from a previously existing sebaceous adenoma (sebaceous lymphadenoma). The remaining cases were either de novo lesions or mixed carcinomas.

Because of the rarity of primary sebaceous carcinomas in the salivary glands, little is known of the behaviour of these tumours. Whether or not their biological course is like that ascribed for sebaceous carcinomas arising outside of the eyelids, caruncles, or orbits cannot be stated at this time.

The possibility that certain basaloid and membranous adenomas can give rise to adenoid cystic carcinomas has been suggested by occasional reports of such hybrid tumours.[34,35] A common putative cell of origin, the replacement cell of the isthmus or terminal tubules, as well as the multilayered basal lamina found in adenoid cystic carcinomas and some membranous adenomas can be regarded as circumstantial evidence. A similar conjecture can also be made for a histogenic relationship between tubular patterns of adenoid cystic carcinoma and trabecular forms of basaloid adenoma. The tubular adenoid cystic carcinoma is the best differentiated and manifests a better prognosis than the other histologic expressions of the carcinoma.[36]

Unequivocal acceptance of the few reported examples of hybrid adenoma/adenoid cystic carcinoma, including the 2 reported previously by the senior author,[33] cannot be made in the light of the identification of the membranous adenoma and dermal analogue tumours in this study. Figures 5–15 to 5–25 in the monograph by Evans & Cruickshank,[35] purporting to illustrate a hybrid carcinoma, fall into the same doubtful category. Absence of recurrences and no microscopic evidence of perineurial invasion in all of the reported cases also require explanation.

In the case of the membranous adenomas and in particular the dermal analogue tumours of cylindroma type, their partial or lack of encapsulation, often prominent deposition of basal lamina and multifocal character can deceive an unwary pathologist into a diagnosis of adenoid cystic carcinoma. A distinguishing feature, should it be needed, is an absence of *perineurial* invasion by any of the dermal cylindroma type salivary adenomas. Perineurial is underscored since just like the cutaneous dermal eccrine cylindroma, there is often a rich association between lobules of tumour and small nerves; even to the point of abuttment of a lobule to the sheath of the nerve (Figure 12). The replicated

basal lamina material in the membranous adenoma and dermal analogue tumours, while obviously sharing biochemical constituents with that found in adenoid cystic carcinomas has a stronger affinity for eosin, is more compact and is distributed in a fashion unlike that found in the so-called cylindromatous type of adenoid cystic carcinoma. In fact, its distribution is identical to that exhibited by the eccrine dermal cylindroma of the skin.[28]

Identification and characterization of the membranous type of monomorphic adenoma should reduce diagnostic confusion between it and adenoid cystic carcinoma. They do not, however, remove from probability, the potential of membranous and basaloid adenomas to be precursors for carcinoma.

References

1 Kleinsasser O. & Klein H.J. (1967) Basalzelladenome der Speicheldrüsen. *Arch. Klin. Exp. Nas. Kehlk. Heilk.* 189, 302.

2 Thackray A.C. & Sobin L.H. (1972) *Histologic Typing of Salivary Gland Tumors.* World Health Organization, Geneva

3 Seifert G. & Schulz C.-P. (1979) Das monomorphe Speichelgangadenom. Klassifikation und Analyse von 79 Fällen. *Virchows Archiv (Pathol. Anat.)* 383, 77

4 Batsakis J.G. (1980) Salivary gland neoplasia: An outcome of modified morphogenesis. *Oral Surg. oral Med. oral Pathol.* 49, 229

5 Young J.A. & VanLennep E.W. (1978) *The Morphology of Salivary Glands*, pp. 145–155. Academic Press, London

6 Headington J.T. (1976) Tumors of the hair follicle. *Am. J. Pathol.* 85, 480

7 Reidbord H.E., Wechsler H.L. & Fisher E.R. (1971) Ultrastructural study of basal cell carcinoma and its variants with comments on histogenesis. *Arch. Dermatol.* 104, 111

8 Regezi J.A. & Batsakis J.G. (1977) Histogenesis of salivary gland neoplasms. *Otolaryngol. Clin. North Am.* 10, 297

9 Cohn R.H., Banerjee S.D. & Bernfield M.R. (1977) Basal lamina of embryonic salivary epithelia: Nature of glycosaminoglycan and organization of extracellular materials. *J. cell Biol.* 73, 464

10 Vracko R. (1974) Basal lamina scaffold—anatomy and significance for maintenance of orderly tissue structure. *Am. J. Pathol.* 77, 314

11 Nelson J.F. & Jacoway J.R. (1973) Monomorphic adenoma (canalicular type). Report of 29 cases. *Cancer* 31, 1511

12 Harrison J.D. (1974) Cystic adenoma of a minor salivary gland: a histochemical study. *J. Pathol.* 114, 29

13 Jao W., Keh P.C. & Swerdlow M.A. (1976) Ultrastructure of the basal cell adenoma of parotid gland. *Cancer* 37, 1322

14 Batsakis J.G. (1980) Clear cell tumors of salivary glands. *Ann. Otol. Rhinol. Laryngol.* 89, 196

15 Donath K., Seifert G. & Schmitz F. (1972) Zur Diagnose und Ultrastruktur des tubularen Speichelgangcarcinoms. Epithelial-myopitheliales Schaltstückcarcinoma. *Virchows Archiv (Pathol. Anat.)* 356, 16

16 Headington J.T., Batsakis J.G., Beals T.F., Campbell T.E., Simmons J.L. & Stone W.D. (1977) Membranous basal cell adenoma of parotid gland, dermal cylindromas, and trichoepitheliomas. Comparative histochemistry and ultrastructure. *Cancer* 39, 2460

17 Reingold I.M., Keasbey L.A. & Graham J.H. (1977) Multicentric dermal-type cylindromas of the parotid glands in a patient with florid turban tumour. *Cancer* 40, 1702

18 Kwapien R.P., Giles R.C., Geil R.G. & Casey H.W. (1977) Basaloid adenomas of the mammary gland in beagle dogs administered investigational contraceptive steroids. *J. Natl Cancer Inst.* 59, 933

19 Prioleau P.G., Santa Cruz D.G., Buettner J.B. & Bauer W.C. (1979) Sweat gland differentiation in mammary adenoid cystic carcinoma. *Cancer* 43, 1952

20 McGavran M., Bauer W.C. & Ackerman L.V. (1960) Sebaceous lymphadenoma of the parotid salivary gland. *Cancer* 13, 1185.

21 Eversole, L.R. (1971) Histogenic classification of salivary tumors. *Arch. Pathol.* 92, 433

22 Johns M.E., Batsakis J.G. & Short C.D. (1973) Oncocytic and oncocytoid tumors of the salivary glands. *Laryngoscope* 83, 1940

23 Batsakis J.G. (1979) *Tumors of the Head and Neck. Clinical and Pathologic Considerations*, p. 25. Williams & Wilkins, Baltimore.

24 Foote F.W. & Frazell E.L. (1953) Tumors of the major salivary glands. *Cancer* 6, 1065

25 Eneroth C.-M. (1964) Histological and clinical aspects of parotid tumors. *Acta otolaryngol. scand.* Suppl. 191.

26 Potdar C.G. (1969) Warthin's tumor. *Arch. Surg.* 98, 206.

27 Döbrössy L., Ronay P. & Molnar L. (1972) Malignant papillary cystadenoma lymphomatosum. *Oncology* 26, 457

28 Crain R.C. & Helwig E.B. (1961) Dermal cylindroma (dermal eccrine cylindroma). *Am. J. clin. Pathol.* 85, 480

29 Seifert G., Heckmayr M. & Donath K. (1977) Carcinome in Papillären Cystadenolymphomen der Parotis. Definotion und Differentialdiagnose. *Z. Krebsforsch.* 90, 25

30 Batsakis J.G. (1979) *Tumors of the Head & Neck. Clinical and Pathological Considerations*, p. 64. Williams & Wilkins, Baltimore.

31 Batsakis J.G., Littler E.R. & Leahy M.S. (1972) Sebaceous cell lesions of the head and neck. *Arch. Otolaryngol.* 95, 151

32 MacFarlane J.K., Viloria J.B. & Palmer J.D. (1975) Sebaceous cell carcinoma of the parotid gland. *Am. J. Surg.* 130, 459

33 Bernacki E.G., Batsakis J.G. & Johns M.E. (1974) Basal cell adenoma. *Arch. Otolaryngol.* 99, 84

34 Klima M., Wolfe K. & Johnson P.E. (1978) Basal cell tumors of the parotid gland. *Arch. Otolaryngol.* 104, 111

35 Evans R.W. & Cruickshank A.H. (1970) *Epithelial Tumours of the Salivary Glands*, pp. 67–73. W.B. Saunders, Philadelphia.

36 Perzin K.H., Gullane P. & Clairmont A.C. (1978) Adenoid cystic carcinomas arising in salivary glands. A correlation of histologic features and clinical course *Cancer* 42, 265

Dermal analogue tumours of major salivary glands

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THE World Health Organization's (Thackray and Sobin, 1972) classification of salivary gland tumours separates *adenomas* into two major types: monomorphic and pleomorphic (mixed tumour). The monomorphic adenomas are further subdivided into three groups: (1) adenolymphoma, (2) oxyphilic adenoma, and (3) other types.

While issue can be taken with consideration of adenolymphoma as a monomorphic lesion, both it and oxyphilic (oncocytic) adenoma are non-controversial in their light and electron-optic characteristics and do not usually present diagnostic problems. The tumours included under 'other types' of monomorphic adenomas, on the other hand, lack such definition in histologic criteria and in taxonomy.

Judging from publications relating cytomorphologic variations as well as differences in opinion as to their cellular composition, the 'other' monomorphic adenomas are not a homogeneous class of tumours.

It is our contention that there are definable subsets of tumours within the classification of 'other' monomorphic adenomas. Some of these represent monophasic cellular variants of mixed tumours and others; analogues or even homologues of certain dermal skin tumours.

The eight examples of dermal analogue tumours of the major salivary glands presented in this report provide support for such a consideration.

Clinicopathologic Findings

The cases presented in this report are derived from two sources: the files of the Oral Pathology Department of the Armed Forces Institute of Pathology, Washington, D.C. and from the senior author's consultation service. One of the latter (Case 3) has been previously presented as a case report (Headington *et al.*, 1977).

Table I summarizes several clinicopathologic aspects of the eight cases. Three patients had co-existing tumours of skin at the time of the clinical presentation of their salivary gland tumours. One patient (Case 3) had multiple skin tumours. The skin tumours in all of these patients were dermal eccrine cylindromas. Patient number 3 also had trichoepitheliomas.

Seven of the salivary gland tumours were in the parotid glands; one

TABLE I

SUMMARY OF CASES

Case	Sex/Age (years)	Salivary gland	Co-existing Dermal tumours	Recurrence of salivary gland tumour
1.	M/68	Submandibular	Scalp	Yes; 2½ years
2.	M/74	Parotid	Temple	No
3.	M/70	Parotid	Scalp, face, chest	No
4.	M/54	Parotid	No	No
5.	M/60	Parotid	No	Yes; 1½ years
6.	M/68	Parotid	No	No
7.	M/56	Parotid	No	Yes; 3 years
8.	F/34	Parotid	No	No

was a submandibular gland primary. The salivary gland tumours presented uniformly as asymptomatic, painless, firm masses. The preoperative existence of the salivary gland tumours was not longer than two years in any patient.

Follow-up periods on the eight patients ranged from four years to two months. Three patients have experienced a recurrence of their salivary gland tumours (Cases 1, 5 and 7). These occurred at 2½, 1½ and 3 years respectively.

The tumours presenting in the parotid glands were found in the lateral lobe. Three of the parotid gland tumours were quite superficial in position and appeared just beneath the fascia of the gland. The smallest tumours measured 1·5 cm. in major dimension; the largest, 4·5 cm.

The microscopic appearances of the first six tumours were quite uniform. Only three of the six were encapsulated. The other three tumours (Cases 1, 3 and 5) demonstrated multifocal origin. The tumours in patients 7 and 8 were encapsulated and while many microscopic fields conformed to those found in the first six tumours, each had significant histologic differences. The major feature of difference in tumour number 7 was a prominent squamous and sebaceous cell differentiation (Fig. 1). In tumour number 8, the stroma was largely composed of lymphoid tissue, suggesting origin from entrapped salivary epithelium within a parotid lymph node (Fig. 2).

Under low power light microscopic examination, all of the tumours appeared as deeply basophilic cellular masses. Those without capsules had irregular extensions into adjacent salivary tissue.

With the exception of tumour number 8, the tumours were composed of islands or larger masses of epithelial cells. The islands varied in size and shape. In many areas, the islands resembled separated parts of a jig-saw puzzle (Fig. 3). The islands and larger parenchymal masses were separated from each other either by an eosinophilic hyaline lamina (Fig. 4) or periepithelial sheaths of varying thickness and/or by a loose, fibrovascular stroma.

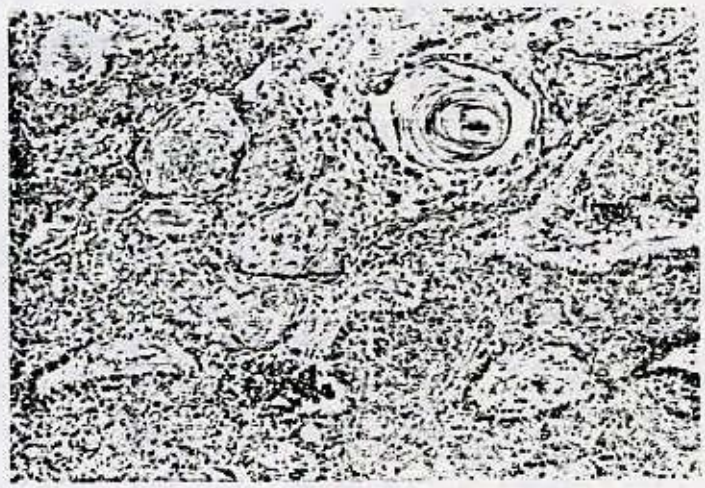

FIG. 1

Dermal analogue tumour (Case 7). Epidermoid differentiation manifested by keratin formation, squamous cells and sebaceous cells is present. Haematoxylin and Eosin ×140.

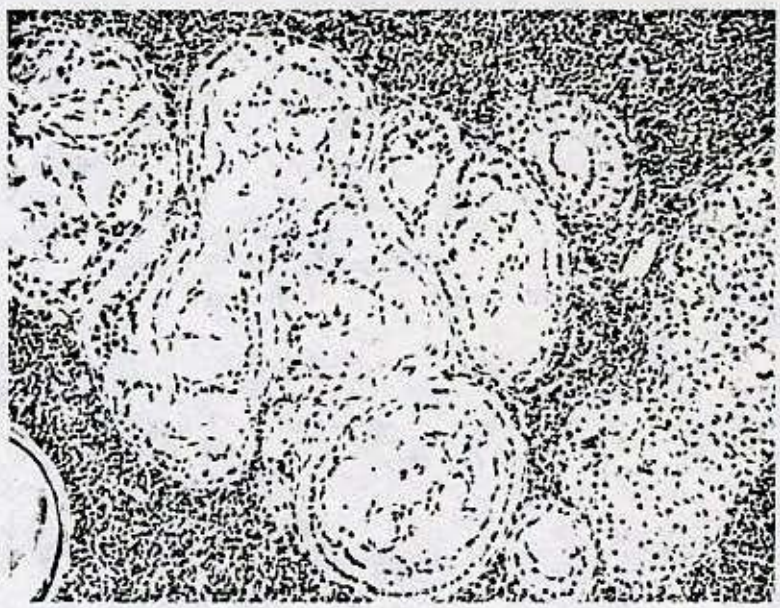

FIG. 2

Dermal analogue tumour (Case 8). Island of hyalinized tumour is set within a lymphoid stroma. Note also the prominent basement membrane around the islands and within where it compresses small tumour cells. Haematoxylin and Eosin ×60.

Aside from delimiting epithelium from stroma, the extracellular hyaline material was deposited in three other forms; (1) hyaline cuffs about blood vessels within the tumours, (2) small droplets surrounded by

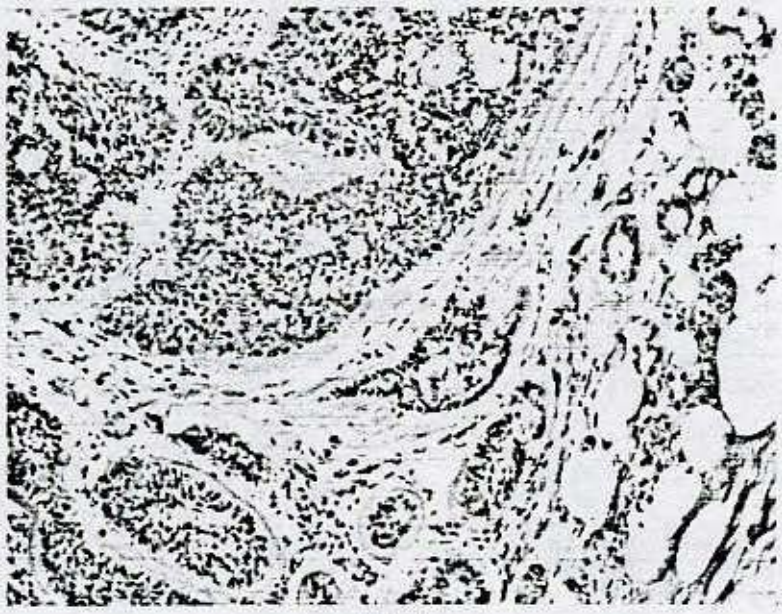

FIG. 3

Dermal analogue tumour (Case 5) extending into adjacent salivary tissue. The epithelial islands contain eosinophilic, extracellular hyaline material and are outlined by a prominent basement membrane. Haematoxylin and Eosin ×40.

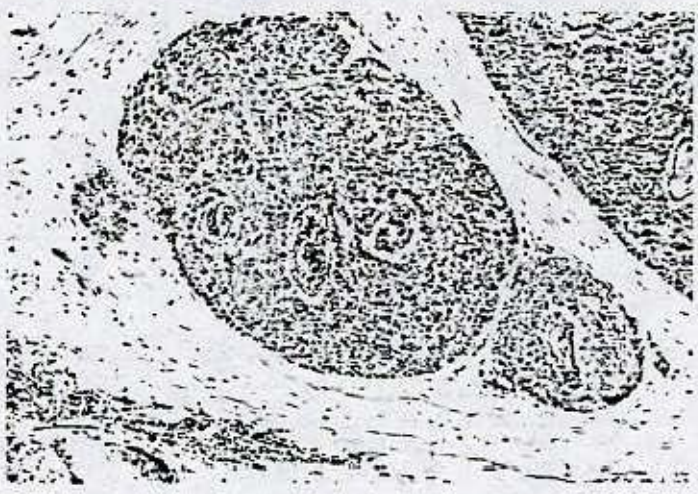

FIG. 4

Typical appearance of the majority of fields in the dermal analogue tumours as seen in Case 6. Islands of epithelial cells are delimited by a thin basal lamina. The smaller, darker cells are at the periphery where they tend to palisade. Haematoxylin and Eosin ×100.

epithelial cells (Fig. 5), and (3) larger coalescent masses entrapping pyknotic cells. Wherever it occurred, the eosinophilic hyaline was PAS-positive, diastase resistent, indicating a mucopolysaccharide content.

FIG. 5

Dermal analogue tumour (Case 1) which closely resembles the dermal eccrine cylindroma of skin. Note the peculiar, yet typical, distribution of the extra-cellular hyaline in the centre of an epithelial island. Haematoxylin and Eosin ×80.

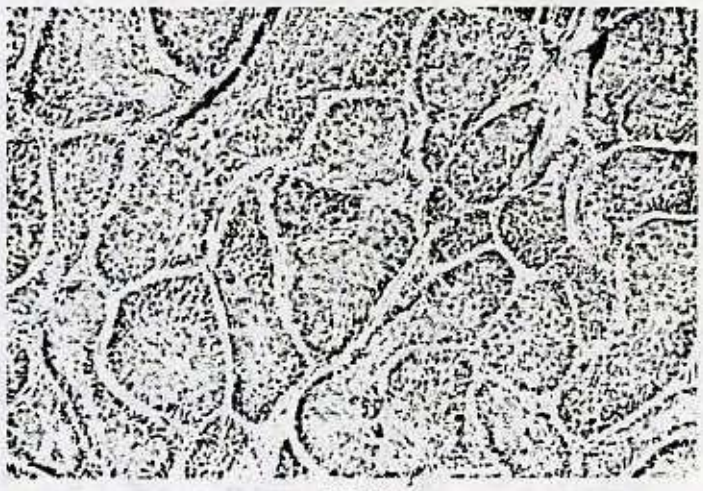

FIG. 6

Dermal analogue tumour (Case 2) with only focal extra-cellular hyaline deposition. Note the whorled appearance of the cells in the centre of the islands and the periepithelial membrane. Haematoxylin and Eosin ×60.

The epithelial islands or masses were composed primarily of two cell types: small, lymphocyte-sized cells with deeply basophilic nuclei and scant cytoplasm and larger cells with paler staining nuclei. The former were most prominent at the periphery of the epithelial masses and often were arranged in a palisade fashion (Fig. 6). These cells were also those most closely related to the extracellular hyaline material. The larger cells were more centrally placed and often assumed a polygonal, plump,

fusiform shape. If the latter dominated, a squamoid whorl filled the centre of an epithelial island (Fig. 6). True squamous differentiation was present only in one tumour (Case 7). Tubular differentiation could be identified in all of the tumours, although it was inconspicuous. The tubules were lined by a single layer of low ductal cells or by a double-layered epithelium.

Despite proximity of the tumours to branches of the VIIth nerve, an invasion of nerves was not found in any of the tumours. At times, however, an epithelial island abutted onto the connective tissue surrounding a small nerve branch.

Discussion

The 'other' monomorphic adenomas of salivary tissues were retrieved from a relative obscurity only during the past decade (Kleinsasser and Klein, 1967; Batsakis, 1972). Formerly, they were included with mixed tumours in classifications. The qualifying adjective—monomorphic—was intended to signify an absence of histologic features associated with mixed tumours (myxoid or chondroid stroma, or cartilage). This absence, and the presence of a basal lamina (basal membrane) about the cell masses were proposed as major diagnostic aids.

After the original reports, a surfeit of studies dealing with various clinical and pathologic aspects of monomorphic adenomas appeared in the literature. In the event, the original, rather circumscribed clinicopathologic delimitations of the tumours have become blurred and definitely broadened. 'Monomorphic' has been interpreted to mean isomorphic or unicellular, and basal cell adenoma translated as synonymous with all monomorphic adenomas. Both interpretations are inaccurate.

Several aspects of the tumours certainly dictate they are not stereotyped. Not only are architectural variations recognized (solid, tubular, trabecular, canalicular), so are variations in cellular composition (Crumpler *et al.*, 1976). The lack of myoepithelial cells in these lesions, once considered a distinguishing feature (Hübner *et al.*, 1971), is now debatable. Jao *et al.* (1976) have described four cell types in the two examples they studied with the electron microscope. Myoepithelial cells were present, as were squamous, secretory, and intermediate cells. The prominence of the basal lamina in the tumours has also varied. Some authors describe a thin limiting membrane, others a multilayered structure (Min *et al.*, 1974).

Even if one allows for possible sampling errors in reported ultrastructural studies of monomorphic adenomas, the observed differences in cellular composition and extracellular products point to definable subsets within monomorphic adenomas. The recent subclassification (Table II) by Seifert and Schulz (1979) is a recognition of the variations possible but is not a denouement. Similar taxonomic evolutions are found in assessments of tumours of skin appendages (Headington, 1976).

Recognition of at least an analogy between tumours of salivary glands and those of skin is not new but is nearly confined to *adenomas* of salivary

TABLE II

CLASSIFICATION OF MONOMORPHIC ADENOMAS
(Seifert and Schulz, 1979)

Cystadenolymphoma
Oncocytoma
Monomorphic adenomas (other types)
Salivary duct
Basal cell
Sebaceous lymphadenoma
Clear-cell adenoma
Mucus-producing adenoma

glands. Kleinsasser and Klein (1967) regarded their basal cell adenomas as analogous to certain cutaneous basal cell growths. Crumpler *et al.* (1976) emphasized the resemblance of monomorphic adenomas to basaloid sweat-gland tumours. A biphasic pattern with close similarities to dermal apocrine adenomas and to salivary basal cell adenomas in certain adenoid cystic carcinomas of the breast has also been reported (Prioleau *et al.*, 1979). The histomorphologic relationship of the chondroid syringoma of skin to mixed tumours of salivary glands (Varela-Duran *et al.*, 1979) further extends the comparisons. Of a more convincing nature, however, is the occasional patient who manifests synchronous or metachronous dermal adenexal tumours *and* variants of monomorphic adenomas in salivary tissues. This diathesis was first reported by Headington *et al.* (1977) and substantiated by Reingold *et al.* (1977). Three of the patients in this report, including the patient reported earlier by Headington *et al.* (1977) are victims of this diathesis; the other patients manifested salivary gland tumours only.

With or without clinical evidence of a diathesis, which may be tentatively regarded as a skin-salivary gland tumour syndrome, the tumours in our eight patients call for an expansion of the WHO classification of the 'other' monomorphic adenomas (Table III). The salivary duct adenoma in this proposed classification represents the uniphasic (epithelial) counterpart of the pleomorphic adenoma (Fig. 7). It may or may not be mucus-producing. The dermal analogue tumours are the adenomatous tumours formerly called basal cell adenomas. They are distinguished by their close histologic resemblance to counterpart tumours arising from the adenexae of the skin, particularly eccrine units. In particular, their relationship is to the dermal eccrine cylindroma (Crain and Helwig, 1961) with which our eight tumours are analogous. The clear-cell adenoma may also be considered to be analogous with sweat gland tumours or tricholemmomas and the sebaceous lymphadenoma has analogous counterparts in sebaceous gland haematomas of skin.

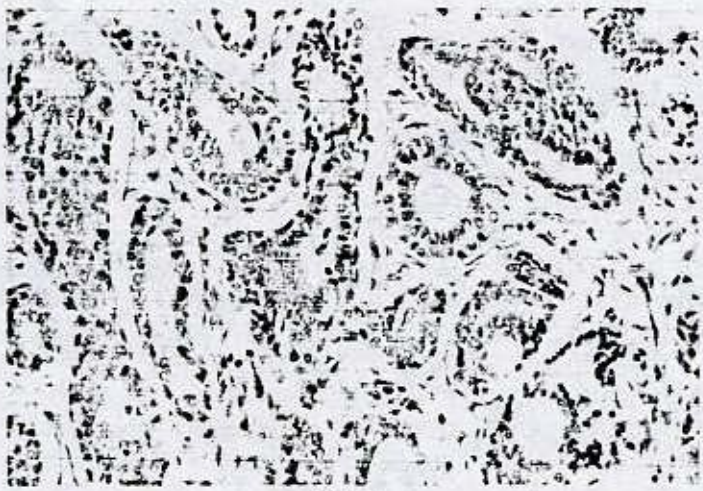

FIG. 7

Monomorphic adenoma of salivary duct type. This form is distinct from the dermal analogue tumours and likely represents a uniphasic pleomorphic adenoma. Haematoxylin and Eosin ×200.

TABLE III

MONOMORPHIC ADENOMAS: HISTOLOGIC CLASSIFICATION

A. *Epithelial*
   1. Salivary duct adenoma (mucous and non-mucous)
   2. Dermal analogue tumours
      (a) Dermal eccrine cylindroma type
      (b) Clear cell adenoma (glycogen positive)
      (c) Sebaceous lymphadenoma
      (d) Others
   3. Dermal homologue tumours (?)

B. *Myoepithelial*
   1. Myoepithelioma
   2. Certain clear cell tumours

We have also proposed the possible existence of dermal *homologue* tumours since selected areas in our tumours were histologically indistinguishable from the dermal eccrine cylindroma (Crain and Helwig, 1961).

The epithelial monomorphic adenomas in Table III manifest histologic features which, to varying degrees, reflect organogenesis of salivary glands. Except for the differentiated salivary duct adenomas, nearly all of the tumours contain areas which recall stages in the embryonic development of the major salivary glands, or at least caricatures of that development. It is pertinent that Headington (1976) has made similar observations for adenexal tumours of skin.

Both the skin adenexae (sweat glands, sebaceous glands, etc.) and salivary glands arise from a germinal epithelium of ectodermal origin

which pushes or 'invades' an investing mesenchyme. Lobular development, tubulo-acinar formation and cytodifferentiation follow during later stages of embryonic life and the early post-natal period.

One of the significant modifiers of salivary gland morphogenesis is the relationship between the epithelial cell mass and the mesenchyme. Mediating the epithelial-mesenchyme interaction is an epithelial derived basal lamina (Bernfield and Banerjee, 1972). In fact, the localization and accumulation of the mucopolysaccharide-containing lamina is likely integral to the final branching morphogenesis and architecture of the salivary glands (Vracko, 1974). In the histologic spectrum of monomorphic adenomas, the basal lamina constitutes one of the variables. It can be delicate and apparently monolayered, or multilayered, aggregated and peculiarly deposited as a prominent extracellular hyaline material. In light of the regulatory importance of the basal lamina, the abnormal growth patterns exhibited by the adenomas can be interpreted as aberrations of a required scaffolding. The multifocal origin of some of our tumours and the exaggerated lobular configuration of most of them can thus be viewed as manifestations of an abnormal framework for epithelial growth.

One other salivary gland tumour is also characterized by peculiar accumulations of a replicated basal lamina—adenoid cystic carcinoma (Tandler, 1971). It is the adenoid cystic carcinoma that is the principal differential diagnosis for dermal analogue monomorphic adenomas. Neoplastic invasion of nerves has not been observed in our tumours or in cutaneous dermal cylindromas (Crain and Helwig, 1961). This is in contrast to the pronounced neurotropism manifested by adenoid cystic carcinomas.

Both adenoid cystic carcinomas and dermal analogue tumours exhibit 'cylinders' of an extracellular hyaline material of which a mucopolysaccharide is a major component. The distribution of this material in dermal analogue tumours and dermal eccrine cylindromas is less orderly and more random than that found in adenoid cystic carcinomas. This is especially true for the small droplets surrounded by individual cells and the larger, coalescent masses found in dermal analogue tumours. A difference in the complete biochemical composition of the laminar material in the two tumours is also suggested by the consistently deep eosinophilic staining of that found in dermal analogue tumours as opposed to the variably staining material in adenoid cystic carcinomas.

The cellular composition and cytologic variations represent the second major variable in monomorphic adenomas as they are currently classified. Since the tumours are believed to arise from the terminal ends of the salivary duct system, i.e., reserve or replacement cells of intercalated ducts, a diversity of phenotypic expression is not unexpected (Regezi and Batsakis, 1977; Batsakis, 1979). The histogenic basis for expression as dermal analogue or homologue tumours, however, remains unexplained.

The biologic behaviour of dermal analogue tumours parallels that of

their counterparts in skin. The 37 per cent recurrence rate (3 of 8 tumours) found in our patients can be compared with the 42 per cent recurrence rate recorded by Crain and Helwig (1961) in their evaluation of dermal eccrine cylindromas. The noted differences in capsule formation, multifocal origin, and extensions into adjacent salivary tissue, afford potential for recurrences in the dermal analogue salivary gland tumours.

Conclusions

Monomorphic adenomas of the major salivary glands manifest a histologic spectrum whose diversity rivals that of pleomorphic adenomas. In nearly all forms of monomorphic adenomas there are histologic features which recall stages in the embryonic development of salivary glands and/or adenexae of skin. A close histogenetic relationship between certain monomorphic adenomas and certain adenexal tumours of skin is suggested by the findings of this report. Within the diversity of expression found in monomorphic adenomas are subsets of tumours which are analogous and nearly homologous with dermal appendage tumours, especially the dermal eccrine cylindroma. The analogous relationship is carried further by a proposed diathesis in which patients exhibit histologically similar tumours in their salivary glands and skin.

'The opinion or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force or Defense.'

REFERENCES

BATSAKIS, J. G. (1972) *Cancer*, **29**, 226.

BATSAKIS, J. G. (1979) *Tumors of the Head and Neck: Clinical and Pathological Considerations*. 2nd Ed., Williams and Wilkins Co., Baltimore.

BERNFIELD, M. R., and BANERJEE, S. D. (1972) *Journal of Cell Biology*, **52**, 664.

CRAIN, R. C., and HELWIG, E. B. (1961) *American Journal of Clinical Pathology*, **35**, 504.

CRUMPLER, C., SCHARFENBERG, J. C., and REED, R. J. (1976) *Cancer*, **38**, 193.

HEADINGTON, J. T. (1976) *American Journal of Pathology*, **85**, 480.

HEADINGTON, J. T., BATSAKIS, J. G., BEALS, T. F., CAMPBELL, T. E., SIMMONS, J. L., and STONE, W. D. (1977) *Cancer*, **39**, 2460.

HÜBNER, G., KLEINSASSER, O., and KLEIN, H. J. (1971) *Virchows Archives of Pathology*, **353**, 333.

JAO, W., KEH, P. C., and SWERDLOW, M. A. (1976) *Cancer*, **37**, 1322.

KLEINSASSER, O., and KLEIN, H. J. (1967) *Archiv für Klinische und experimentelhe Ohren-, Nasen- und Kehlkopfheilkunde*, **189**, 302.

MIN, B. H., MILLER, A. S., LEIFER, C., and PUTONG, P. B. (1974) *Archives of Otolaryngology*, **99**, 88.

PRIOLEAU, P. G., SANTA CRUZ, D. J., BUETTNER, J. B., and BAUER, W. C. (1979) *Cancer*, **43**, 1752.

REGEZI, J. A., and BATSAKIS, J. G. (1977) *Otolaryngologic Clinics of North America*, **10**, 297.

REINGOLD, I. M., KEASBEY, L. E., and GRAHAM, J. H. (1977) *Cancer*, **40**, 1702.

SEIFERT, G., and SCHULZ, C. P. (1979) *Virchows Archives of Pathology*, **383**, 77.

TANDLER, B. (1971) *Laboratory Investigation*, **24**, 504.

THACKRAY, A. C., and SOBIN, L. H. (1972) *WHO*, Geneva.

VARELA-DURAN, J., DIAZ-FLORES, L., and VARELA-NUNEX, R. (1979) *Cancer*, **44**, 148.

VRACKO, R. (1974) *American Journal of Pathology*, **77**, 314.

Case 4. Submandibular gland, low-grade myoepithelial carcinoma

This peculiar lobular neoplasm of salivary gland has a somewhat varied appearance, ranging from clear cells and clear cells about ducts to solid lobular masses without clear cells. The clear cell areas are entirely consistent with epithelial-myoepithelial carcinoma of intercalated ducts. The solid areas are also similar to epi-myoepithelial proliferations I've seen in other tumors.

Your case was not immunoreactive with antibodies to myosin, keratin, or S-100 protein antigen which would have been helpful for definition of the cellular composition.

Nonetheless, I classify this neoplasm as a epi-myoepithelial carcinoma on the basis of the aforementioned clear cells, lobular growth pattern and infiltration with nerve invasion. It belongs to a recently emerging group of salivary carcinomas in which the enigmatic myoepithelial cell is the preponderant cell.

Our experience with these neoplasms is limited but we are impressed with the relatively high recurrence rate and local extension manifested by myoepithelial dominant salivary tumors.

The two accompanying reprints attest to this.

THE PATHOLOGY OF HEAD AND NECK TUMORS: THE MYOEPITHELIAL CELL AND ITS PARTICIPATION IN SALIVARY GLAND NEOPLASIA, PART 17

JOHN G. BATSAKIS, MD, BEVERLY KRAEMER, MD, and JAMES J. SCIUBBA, DMD, PhD

Abstract: Sharing a common ectodermal origin with salivary duct epithelium, the myoepithelial cell is two-sided in several respects. It lies between the epithelial cells and the basal lamina, with one side facing the duct or acinar cells and the other facing the stroma. It has a fine structure not unlike that of smooth muscle, and one of its functions is to contract. Despite its electron-optic similarity to smooth muscle, the myoepithelial cell's principal filamentous protein is cytokeratin, which is found only in epithelial cells. Myoepithelial cells do not have a demonstrable secretory capability, but they can store glycogen in abundance. In some tumors of the salivary glands, myoepithelial cells do not participate in histogenesis. These tumors arise from portions of the salivary duct system in which myoepithelial cells are not normally found. In tumors originating from intercalated ducts, myoepithelial cells may assume one of two roles; a passive presence or an active and integral formation of the tumors. Mixed tumors, clear cell tumors, plasmacytoid (hyaline cell) and fibroblastic myoepitheliomas, and terminal duct adenocarcinomas are examples of tumors in which the myoepithelial cell is prominent or dominant.

HEAD & NECK SURGERY 5:222–233 1983

One of the definitions of conundrum is "a riddle turning on some odd or fanciful resemblance between things quite unlike."[1] Nearly everything about the myoepithelial cell—its origin, function, and putative role in the histogenesis of salivary gland tumors—fits this definition.

Myoepithelial cells have fascinated scores of investigators, each of whom has contributed valuable information, albeit at times contradictory. Even with the use of contemporary histochemical, immunochemical, and electron-optic technics, however, the myoepithelial cell remains elusive, especially in its neoplastic panoply.[2-5]

With the notable exception of the pancreas, myoepithelial cells have been found in nearly all exocrine glands, such as the sweat glands, breast, Bartholin's glands, mucous glands of the trachea and esophagus, and the prostate gland.[6] The cells are present in the parenchymal elements of all mammalian salivary glands (including lacrimal) that have been studied.

In salivary glands, the myoepithelial cells are associated with intercalated ducts (Fig. 1) and usually with acini. Their number and distribution about the secretory endpieces of the gland varies according to the species and the specific

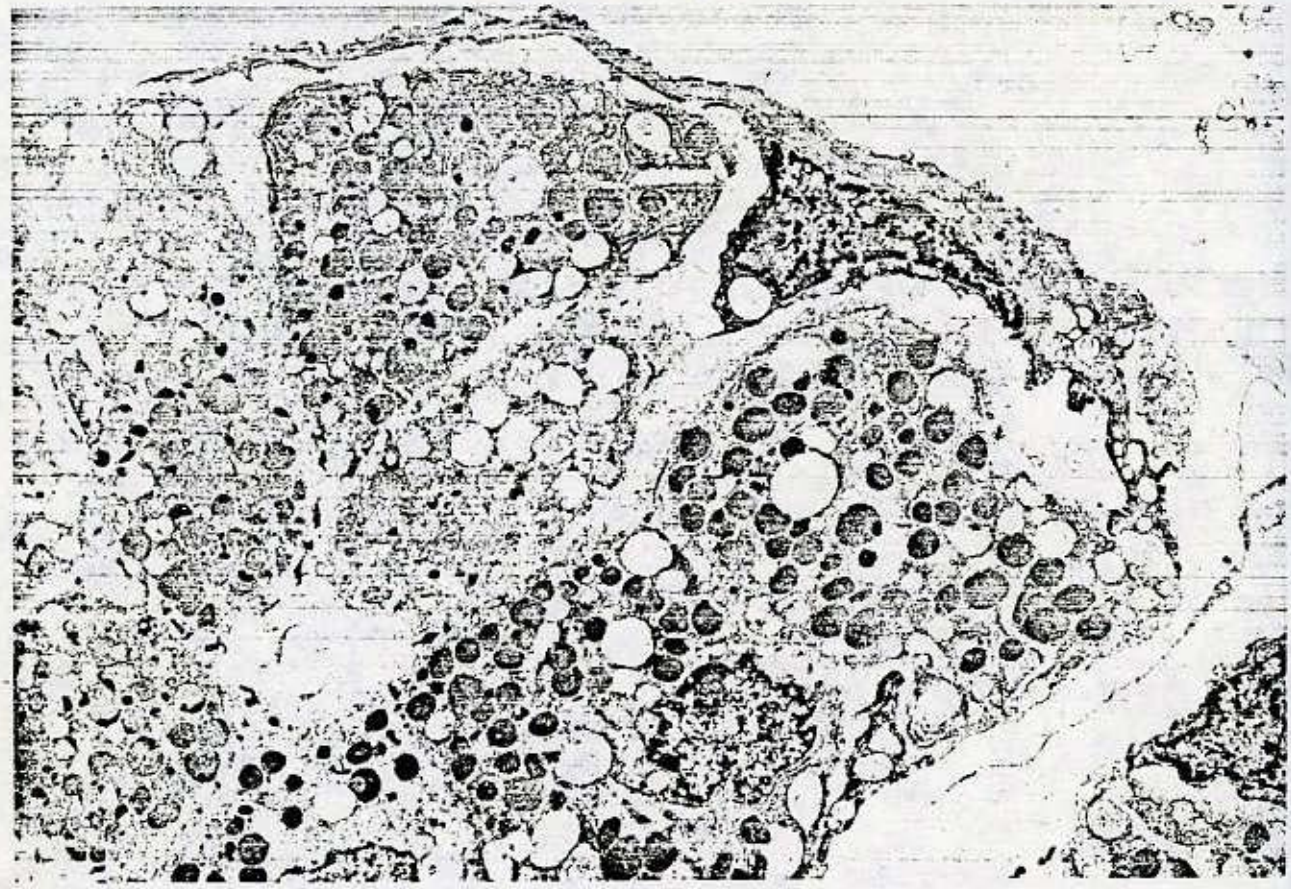

Figure 1. Electron micrograph of acinar cells (left) and a surmounting myoepithelial cell whose processes embrace two of the acinar cells. ×5,300.

salivary gland.[3,5] In the rat submandibular gland, myoepithelial cells make up almost 10% of the intralobular parenchyma, 12.5% of the acinar volume, and 40% of the intercalated duct volume.[7] In most salivary glands, the myoepithelia embrace the acini and intercalated ducts and usually do not have a conspicuous relationship with the striated ducts. Processes of the cells, however, can be seen passing on to the beginning of the striated ducts adjacent to the intercalated ducts. The shape of the cells differs according to their location. On acini, they assume a basket-like configuration; those on the ducts are spindle-shaped.[3,5]

MICROSCOPIC CHARACTERISTICS

Light optic identification of myoepithelial cells, until recently, has been based on the position and shape of the cells and on several histochemical reactions. Of the histochemical technics, those employed to demonstrate alkaline phosphatase and adenosine triphosphatase (ATPase) have been most commonly used. Neither of these enzymes can be used as a general marker for myoepithelial cells.[3] Both exhibit interspecies variation. Alkaline phosphatase activity is not limited to myoepithelia, and there are great quantitative and qualitative differences in the enzyme content of the plasma membranes of salivary myoepithelium; not only between glands but also between species. ATPase reaction products are localized on the plasma membrane of cells; the reaction is positive in human myoepithelial cells but negative in those of cats and dogs.[3]

The normal salivary gland myoepithelial cell has been well defined by electron microscopists.[3,5,6,8] The cells show a separation of their cytoplasm into two main compartments. One is nonfilamentous and the other contains filaments (Fig. 2). The nucleus and organelles are found in the nonfilamentous part. Golgi complexes are usually situated close to the nucleus, and a few cisterns of rough endoplasmic reticulum, unattached ribosomes, and lysosome-like bodies are present. Mitochondria are not frequent and are found in the perikaryon and cell processes. Glyco-

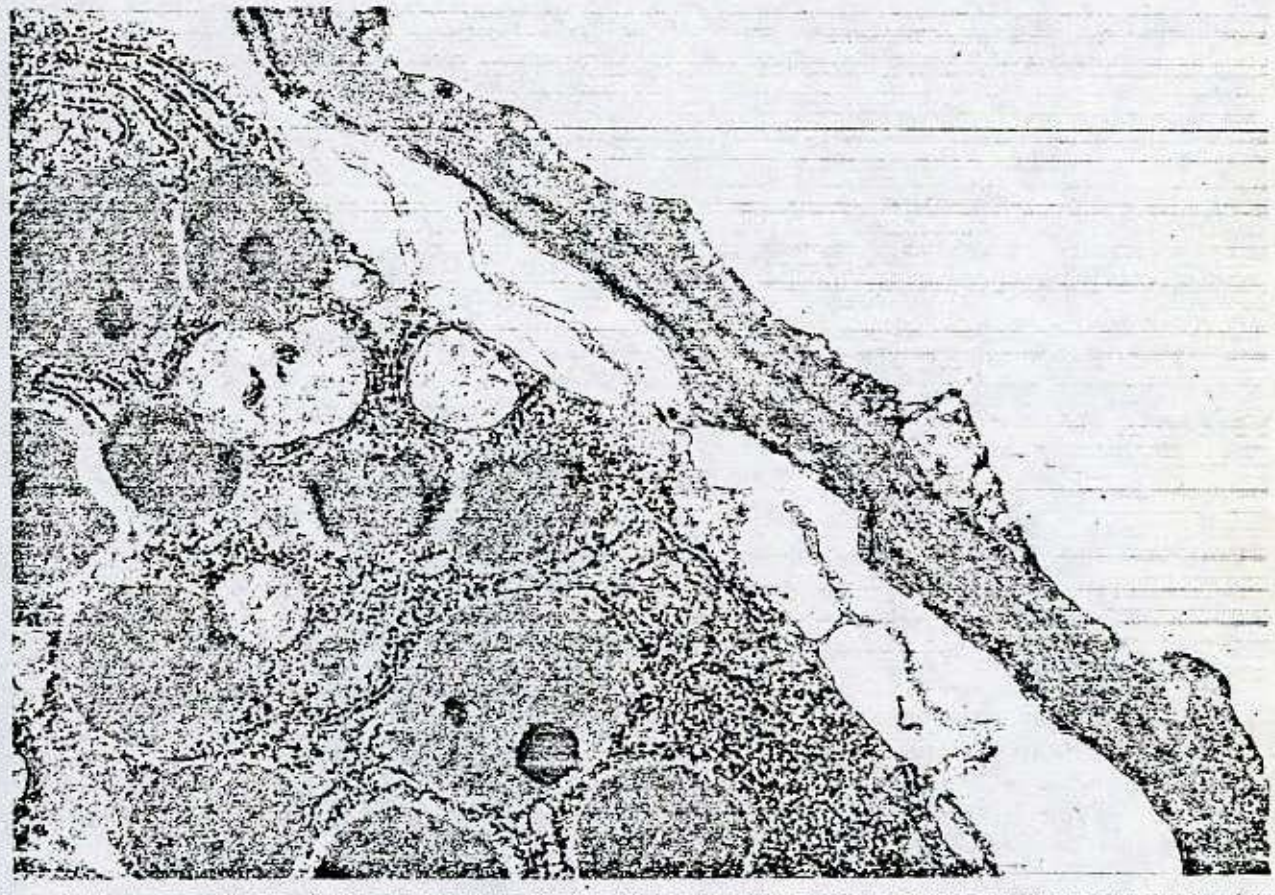

Figure 2. Higher magnification of the myoepithelial-epithelial relationship shown in Figure 1. Note the filamentous quality of the cytoplasm of the myoepithelial cell and the cell junction in the center of the field. ×27,000.

gen and a few neutral fat globules are found, but no secretory product is present.

The most conspicuous components are filaments which fill the greater part of the cells. These resemble the myofilaments of smooth muscle. There are two varieties of filaments. Most are thin (approximately 4 nm in diameter) and usually occupy the space near the basal lamina. Thicker filaments, on the order of 10 nm in diameter, are also scattered among the thinner filaments. Although true hemidesmosomes are not seen on the stromal surface, filaments appear to be specifically attached there to plaques. Desmosomal attachments between myoepithelial cells with secretory cells are present, but are usually widely spaced. The stromal plasma membranes of myoepithelial cells usually contain open caveolae in clumps irregularly dispersed along the surface. Fewer caveolae tend to be present on the epithelial face of the cells. These caveolar invaginations are apparently what some investigators call pinocytotic or micropinocytotic vesicles.

Two features of the cells, their cytoplasmic filaments and their contractility, have been used by protagonists to indicate a mesenchymal rather than an epithelial derivation of the cells. Advances in electron microscopy and immunocytochemistry have forced a reassessment. The immunochemical evidence is such that an epithelial and nonmesenchymal lineage can be ascribed to the myoepithelial cell.

MYOEPITHELIAL CELL FILAMENTS

The cytoplasm of mammalian cells contains an impressive array of filamentous proteins.[9,10] These proteins play a role in several cellular functions: *(1)* maintenance of shape, *(2)* motility and cytokinesis, *(3)* modulation of cell membrane movement, *(4)* mobility of chromosomes and cell processes, and *(5)* regulation of cell proliferation and organogenesis.

Table 1. Filamentous proteins (intermediate-sized fibers) in human cells

Type of cell	Major filamentous protein	Comment
Smooth muscle	Desmin (skeletin)	Also in skeletal and cardiac muscle
Epithelial	Prekeratin-like (cytokeratin)	Found in nearly all true epithelia
Nonmuscle mesenchymal	Vimentin	—
Neuronal	Neurofilament protein	—
Glial	Glial filament protein	—
Myoepithelial	Prekeratin	Cells are not specifically stained by antibodies to vimentin or desmin

Myoepithelial cells show an organization of filaments that is reminiscent of that observed in smooth muscle cells. They also contain large amounts of actin-containing microfilament bundles, along with tropomyosin and myosin, "dense bodies," and endocytotic vesicles. Of particular interest is the rather intricate network of filaments of intermediate thickness (7–11 nm). These filaments are not unlike the arrays of filaments found in smooth muscle. In smooth muscle, the filaments contain one major protein—desmin or "skeletin."[9,10]

Actin and myosin have been demonstrated in an increasing number of nonmuscle cells.[11,12] In such cells, the proteins are thought to be involved in various activities of mobility. In particular reference to salivary tissues, positive immunocytochemical reactions for actin and myosin occur at three principal sites: most intense in myoepithelial cells, less so in secretory epithelial cells beneath the cell membrane bordering acinar lumina, and in a similar location in excretory, striated, and intercalated ducts.

Intermediate-sized filaments are also found in epithelial cells, where their major protein is a prekeratin-like protein or cytokeratin.[9,10,11,13] The major, if not exclusive, protein in filaments found in nonmuscle mesenchymal cells is vimentin.[9]

Cytokeratin is found in nearly all true epithelial cells.[14] In contrast, nonepithelial cells do not contain intermediate-sized filaments of the cytokeratin type.[9,14] Thus, it can be seen that filaments of the cytokeratin type, together with an absence of intermediate filaments of the vimentin type, and of significant amounts, if any, of the desmin type, provide good objective criteria by which to distinguish epithelial from mesenchymal-muscle cells. Table 1 presents the major or exclusive filamentous proteins found in myoepithelial cells and other tissues.

Immunocytochemical and electron optic evidence seriously damages any thesis that supports a nonepithelial origin for myoepithelia. The work of Franke and associates[9,10] also suggests that in the myoepithelial cell, prekeratin filaments are arranged and conceivably function like desmin filaments in smooth muscle, even though desmin and desmin-containing filaments are specific for myogenic differentiation.

Differentiation of myoepithelial cells is best explained in relation to the overall morphogenesis of the salivary gland, especially the salivary duct unit.[15,16] Figure 3 displays this system in schematic form. The entire salivary duct unit is derived from ectoderm (epithelial). Stem cells in the primordium differentiate into the various components of the duct unit, including the secretory endpieces and myoepithelium.[15–18] Replenishment of the cells in the postnatal state is considered to come from committed reserve cells, those of the intercalated duct providing the intercalated duct and acinar cell replacements.[16] It is possible that a separate cell line is responsible for myoepithelial cells, but there is no convincing evidence that the cell line is other than epithelial. In its earliest recognizable state, the myoepithelial cell is in a peripheral position and subjacent to the basal lamina. The maturation process of the cell is primarily characterized by

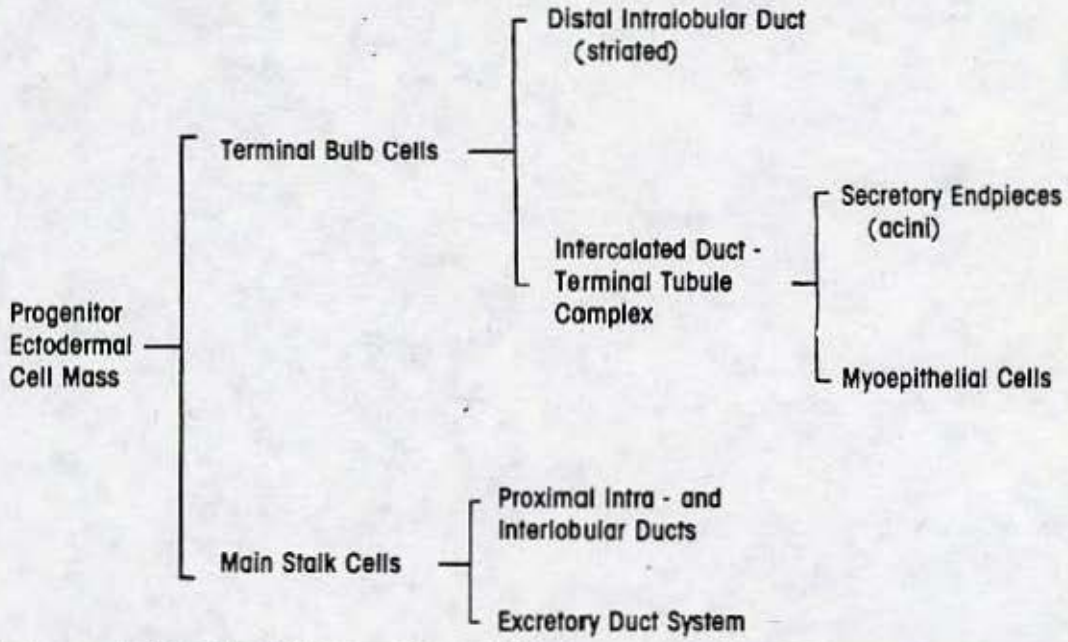

Figure 3. Morphogenesis of the salivary duct system. Myoepithelial cells are presumed to arise from precursor cells in the intercalated duct-terminal tubule complex.

accumulation of microfilaments in the peripheral cytoplasm. At no time, either during development or at maturity, are secretory granules found in myoepithelial cells. Table 2 summarizes the salient features of salivary gland myoepithelial cells.

Table 2. Salivary gland myoepithelial cells.

Location	
Always on the epithelial side of basal lamina	
Associated with secretory endpieces (acini and intercalated ducts)	
Function	
Contractile	
No known secretory activity	
Histochemical reactions	
Alkaline phosphatase: nonspecific,species dependent	
Adenosine triphosphatase: relatively specific, species dependent	
Immunocytochemical reactions	
Actin and myosin:	Lack specificity
Desmin:	Negative
Vimentin:	Negative
Prekeratin (cytokeratin):	Positive
Ultrastructure	
Cytofilaments	
Desmosomes and hemidesmosomes	
Single cilium (points toward and often inserts into or between adjacent cells)	
Caveolar invaginations (pinocytotic surface specializations)	
Glycogen	

TUMORS WITH MYOEPITHELIAL CELLS

Among the uncertainties regarding the formation of salivary gland tumors, the role of the myoepithelial cells ranks high.[4,19,20] Certainly, these cells may be excluded from tumors that arise proximal to the distal parts of the striated ducts. Recent reports on specific classes of salivary gland neoplasia, however, point to a direct and sometimes apparently exclusive histogenetic role of the cells.[6,21–27]

Figure 4 shows the three principal light optic presentations of myoepithelial cells; *(1)* hyaline or plasmacytoid, *(2)* fibroblastic or myoid, and *(3)* epithelial-like. The last often appears as a clear cell. The mixed tumor (pleomorphic adenoma) is the most common salivary gland tumor in which the myoepithelial cell is a recognized component (Figs. 5 and 6). In this tumor, the myoepithelial cell's phenotypic expression can be hyaline, fibroblastic, or both. Predominance of the cells in mixed tumors varies considerably. In some tumors, myoepithelia are sparse, and these cellular mixed tumors resemble the epithelial monomorphic adenomas in appearance. In other tumors, the mixed tumor is largely composed of myoepithelial cells and stroma, that is, a mixed tumor with myoepithelial dominance. Tumors completely devoid of epithelial cells (usually in the form of ducts) merit the designation myoepithelioma.

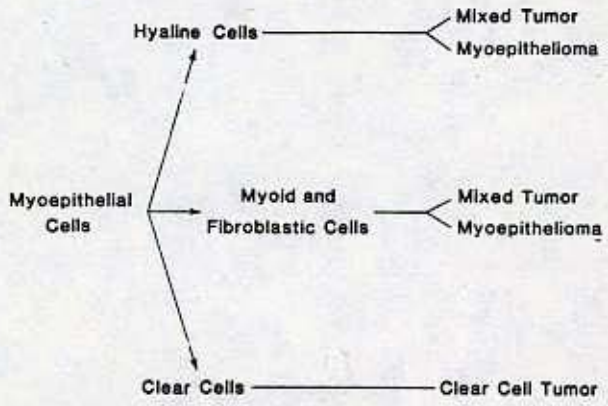

Figure 4. Light optic presentations of myoepithelial cells and tumors in which each type participates.

All of the tumors with significant myoepithelial participation arise from the distal end (toward the acini) of the salivary duct unit. Table 3 lists the salivary gland tumors in which we consider the myoepithelial cell to play an active role in histogenesis. Each of the tumors is briefly outlined below.

Mixed Tumors. The cellular derivation of these salivary gland tumors, also called pleomorphic adenomas, has been debated for decades. Whatever its lineage, the myoepithelial cell must play an integral role. Mixed tumors do not occur in tissues in which the myoepithelial cell is absent. Histologically equivalent tumors do arise in extrasalivary exocrine sites, with the singular exception of the pancreas; myoepithelial cells have never been found in the exocrine pancreas.

Tissue culture studies, examination of salivary gland mucins, and ultrastructural analyses

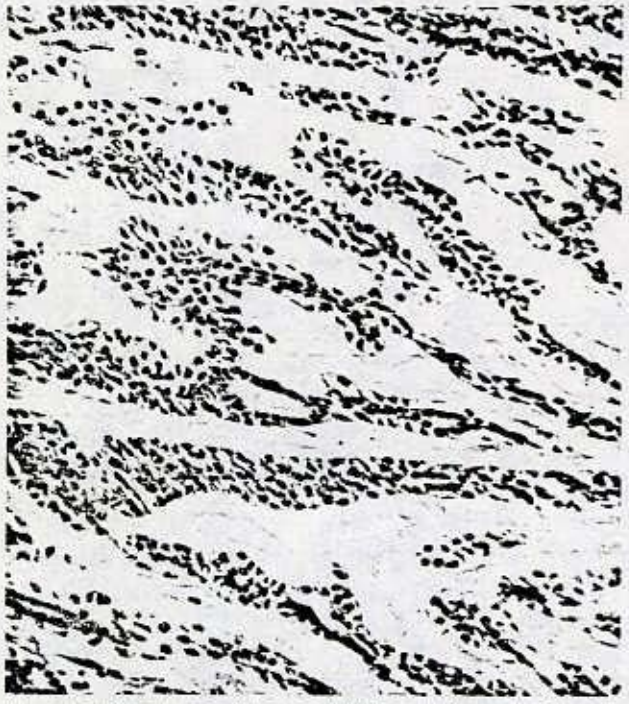

Figure 5. Mixed tumor of the parotid gland. Myoepithelial cells lie at the periphery of the cellular groups, which, in turn, are separated by a hyaline stroma. Hematoxylin and eosin, ×120.

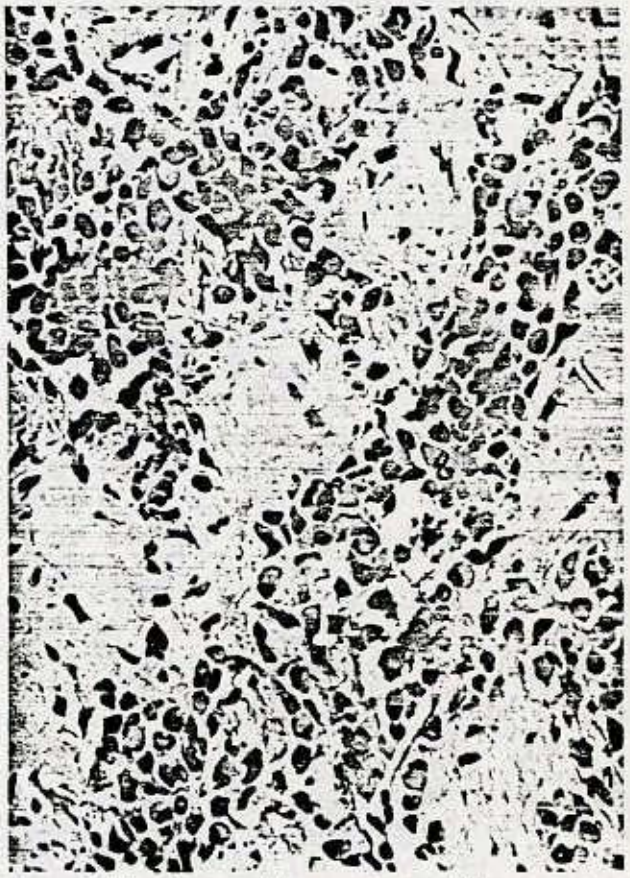

Figure 6. Mixed tumor of the parotid gland. Numerous plasmacytoid myoepithelial cells surround and are invested by a chondroid stroma. Hematoxylin and eosin, ×200.

Table 3. Salivary gland tumors with significant myoepithelial cell participation.

Mixed tumor (pleomorphic adenoma)
Myoepithelioma
Plasmacytoid
Fibroblastic
Mixed
Clear cell tumor
Biphasic (epithelial-myoepithelial carcinoma of intercalated ducts)
Uniphasic (solid myoepithelial clear cell)
Terminal duct adenocarcinoma

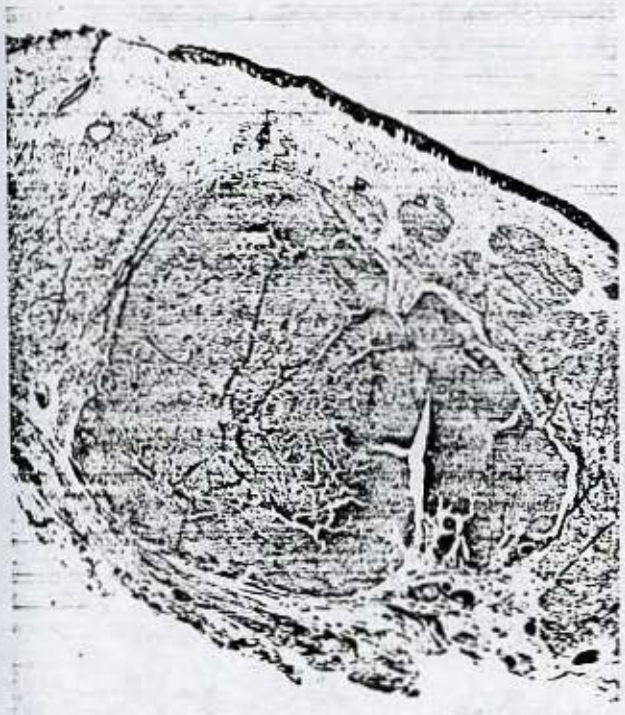

Figure 7. Myoepithelioma of the palate. The tumor is circumscribed but not encapsulated. Hematoxylin and eosin, ×25.

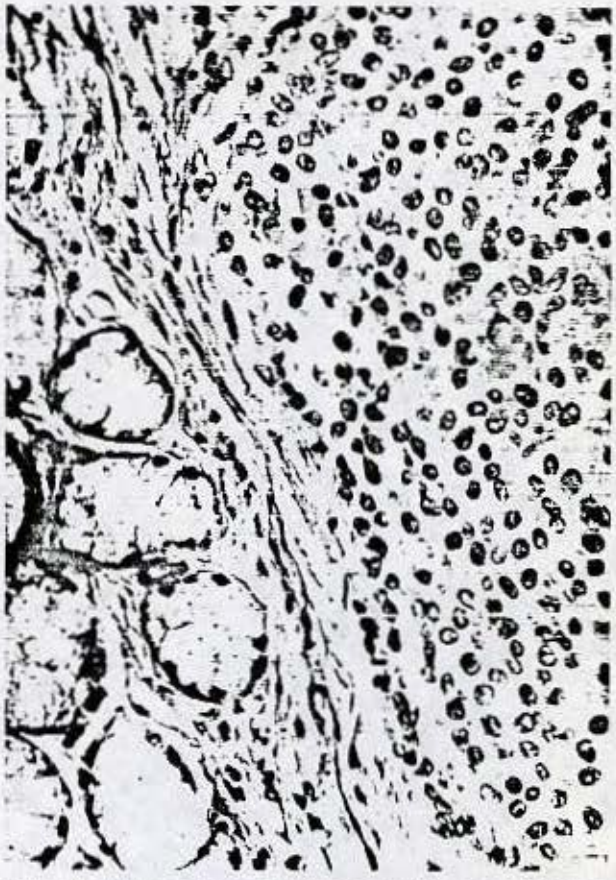

Figure 8. Higher-power magnification of the myoepithelioma shown in Figure 7. Note the resemblance of the cells to plasma cells. Hematoxylin and eosin, ×250.

have all confirmed the importance of the myoepithelial cell in fashioning the often varied histologic appearance of mixed tumors.[28–33] Shirasuna et al.[31] have also discovered a human myoepithelial cell line carrying tumorigenicity.

Plasmacytoid Myoepitheliomas. Tumors apparently composed entirely of plasmacytoid or hyaline myoepithelial cells have a rather strong predilection for intraoral sites, especially the palate.[21–23] Nearly always circumscribed, the tumors are usually devoid of a significant capsule. Their growth pattern can be either one of closely packed cells or one in which the cells are separated by a loosely textured mucoid stroma (Figs. 7–10).

The tumor's biologic behavior is similar to that of the mixed tumors. Unfamiliarity with the lesion occasions misdiagnoses such as extramedullary plasmacytoma, mucoepidermoid carcinoma, or some form of squamous cell carcinoma.

Fibroblastic or Myoid Myoepitheliomas. As the qualifying adjectives for these myoepitheliomas suggest, these tumors appear as supporting tissue lesions.[6,32] For this reason, pathologists may render diagnoses of fibrous, neurogenous, or meningiomatous tumors (Figs. 11–13).

Circumscribed and most often encased in a thin capsule, this form of myoepithelioma is primarily a tumor of major salivary glands, particularly the parotid.

Clear Cell Tumors. We are of the opinion that primary nonmucinous, nonsebaceous clear cell neoplasms of salivary glands should be regarded as carcinomas.[25,26] In its most readily recognized form, the clear cell tumor exhibits a characteristic bicellular histologic appearance (Fig. 14). This light optic presentation prompted the diagnostic term "epithelial-myoepithelial carcinomas of intercalated ducts," a designation encompassing an accurate description and histogenesis (Fig. 15). Various proportions of duct cells and clear

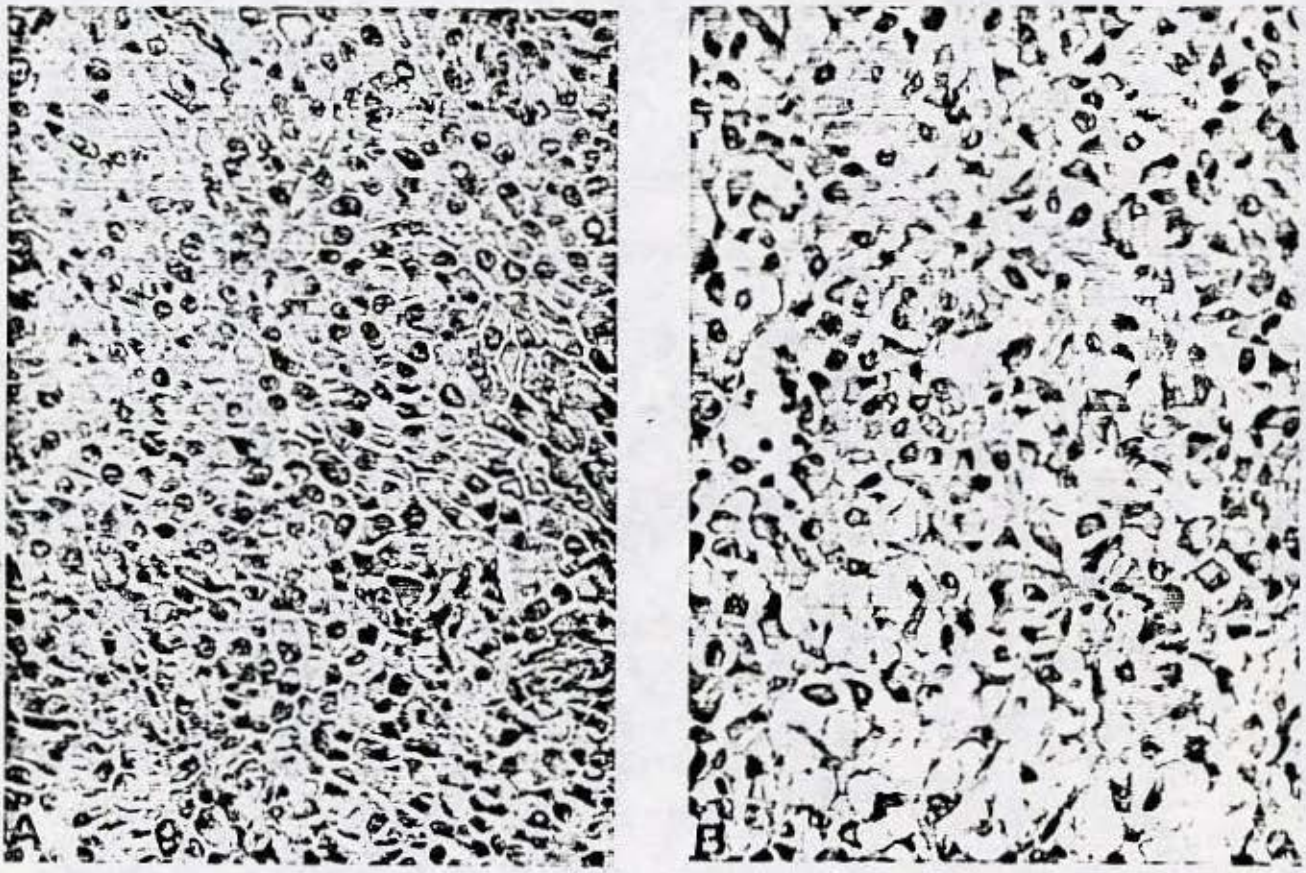

Figure 9. (A, B) Two other myoepitheliomas of the palate. (A) The plasmacytoid or hyaline myoepithelial cells are closely packed and do not have a significant amount of intercellular stroma. (B) The cells are more loosely arranged, and there is a mucoid matrix. (A, B) Hematoxylin and eosin, ×160.

myoepithelial cells are found. At times, solid groups of clear cells are the only neoplastic expression.

Terminal Duct Adenocarcinomas. This distinctive salivary gland malignancy is primarily one of minor salivary tissues, especially within the oral cavity.[27] Unencapsulated and infiltrative, terminal duct adenocarcinomas manifest a pronounced neurotropism, especially for small nerve branches (Figs. 16 and 17).

Never as perceptibly biphasic as the classic form of clear cell carcinomas, terminal duct adenocarcinomas contain both myoepithelial and epithelial components. The former assume a spindle conformation; the latter are small, undifferentiated ducts which resemble embryonic intercalated ducts (Fig. 18).

Two of the four classes of salivary gland tumors listed in Table 3 are carcinomas. With the exception of solid clear cell carcinomas, the others contain prominent ductal components as intrinsic parts of the carcinoma. Pure myoepitheliomas that exhibit other than a benign or locally aggressive course are rare.[6]

SUMMARY

A review of the myoepithelial cell in its normal and neoplastic states has been presented. Recent immunochemical characterization of the cell's intermediate sized filaments such as cytokeratin, along with electron optic features, establish an epithelial rather than a mesenchymal origin for myoepithelia.

Four classes of salivary gland tumors with prominent, if not exclusive, participation by myoepithelial cells are described. These are mixed tumors, clear cell tumors, myoepitheliomas, and terminal duct adenocarcinomas.

The next report in this series will be on papillomas of the upper aerodigestive tracts.

Figure 10. Hyaline, plasma cell-like myoepithelial cells from a myoepithelioma. Hematoxylin and eosin, ×300.

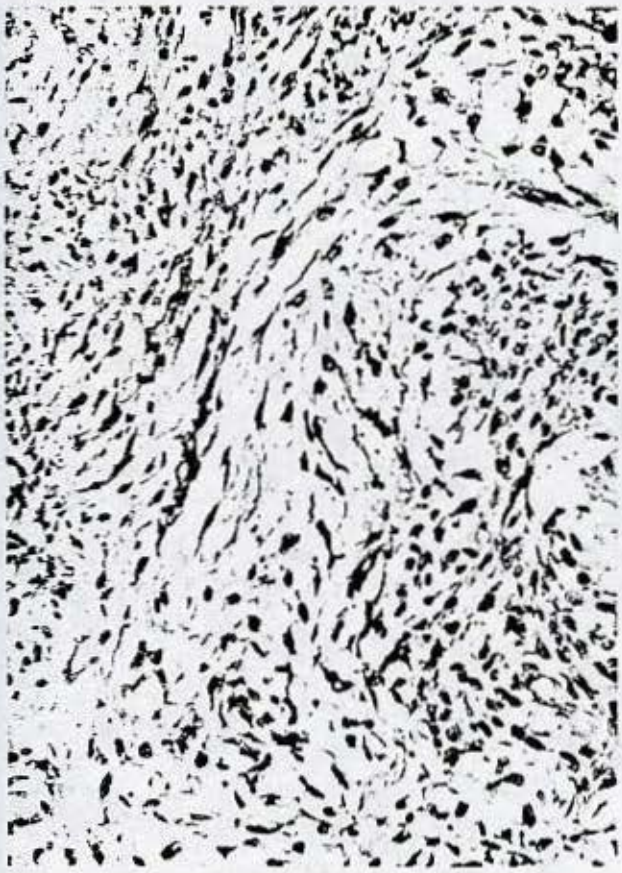

Figure 12. Myoepithelioma of the parotid gland without epithelial participation. Hematoxylin and eosin, ×160.

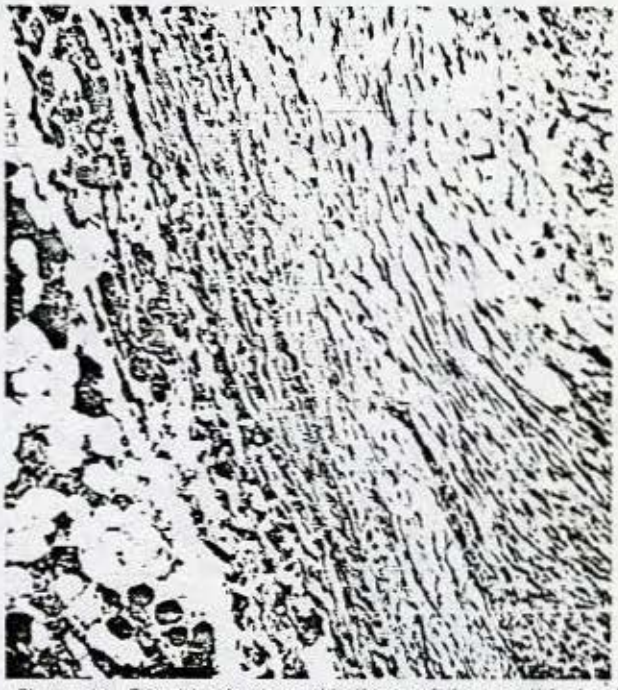

Figure 11. Fibroblastic myoepithelioma of the parotid gland. Note the thin capsule separating the tumor from the uninvolved parenchyma. Hematoxylin and eosin, ×65.

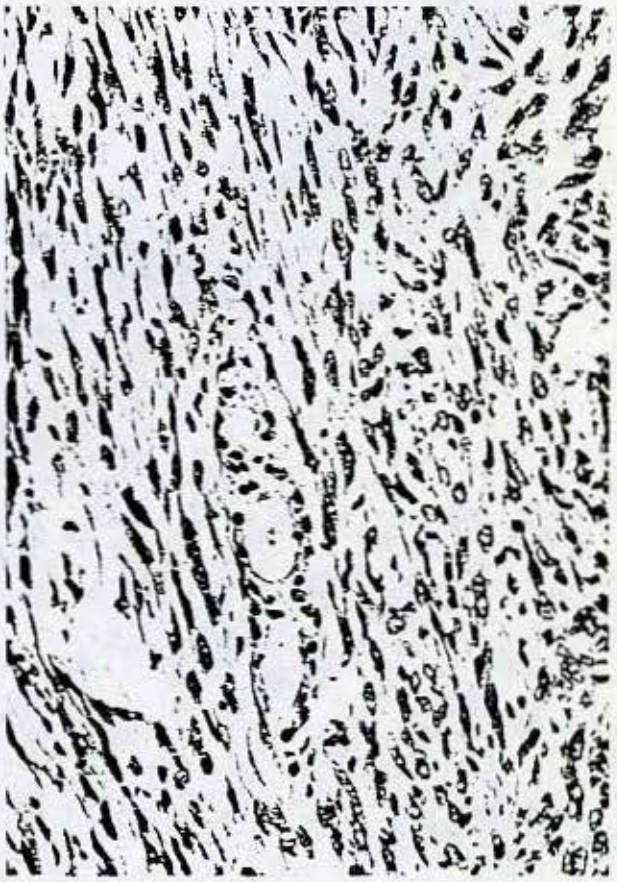

Figure 13. Spindle cells of a predominantly myoepitheliomatous tumor of the parotid gland surrounding ductal elements. Hematoxylin and eosin, ×140.

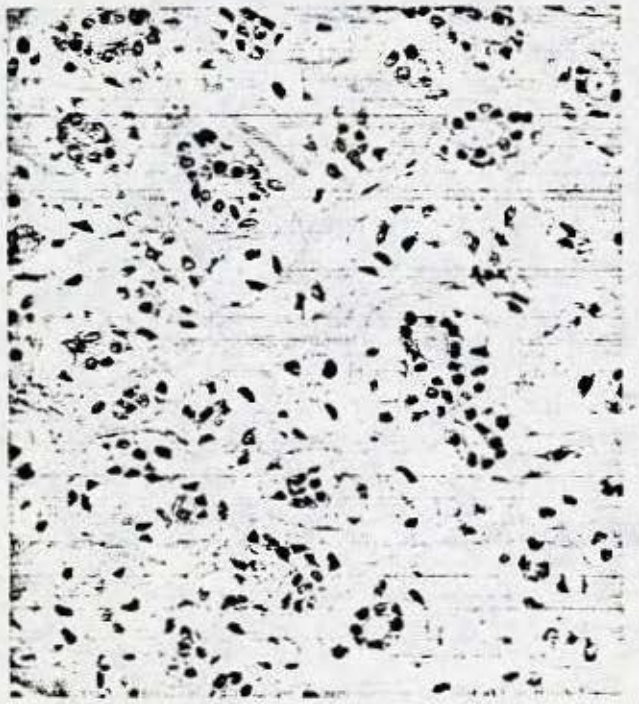

Figure 14. Epithelial-myoepithelial carcinoma of intercalated ducts. This tumor arose in the parotid gland. Hematoxylin and eosin, ×80.

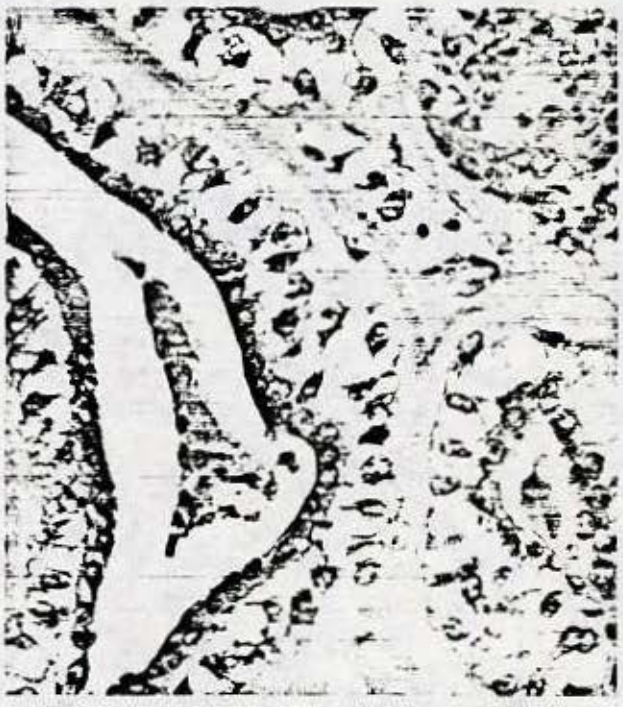

Figure 15. Biphasic pattern of epithelial-myoepithelial carcinoma of intercalated ducts. The myoepithelial cells form an outer clear cell mantle. The clear cells are often glycogen-rich. Hematoxylin and eosin, ×80.

Figure 16. Low-power appearance of a terminal duct adenocarcinoma of the palate. Note the infiltrative growth and extension into the underlying palatal bone. Hematoxylin and eosin, ×15.

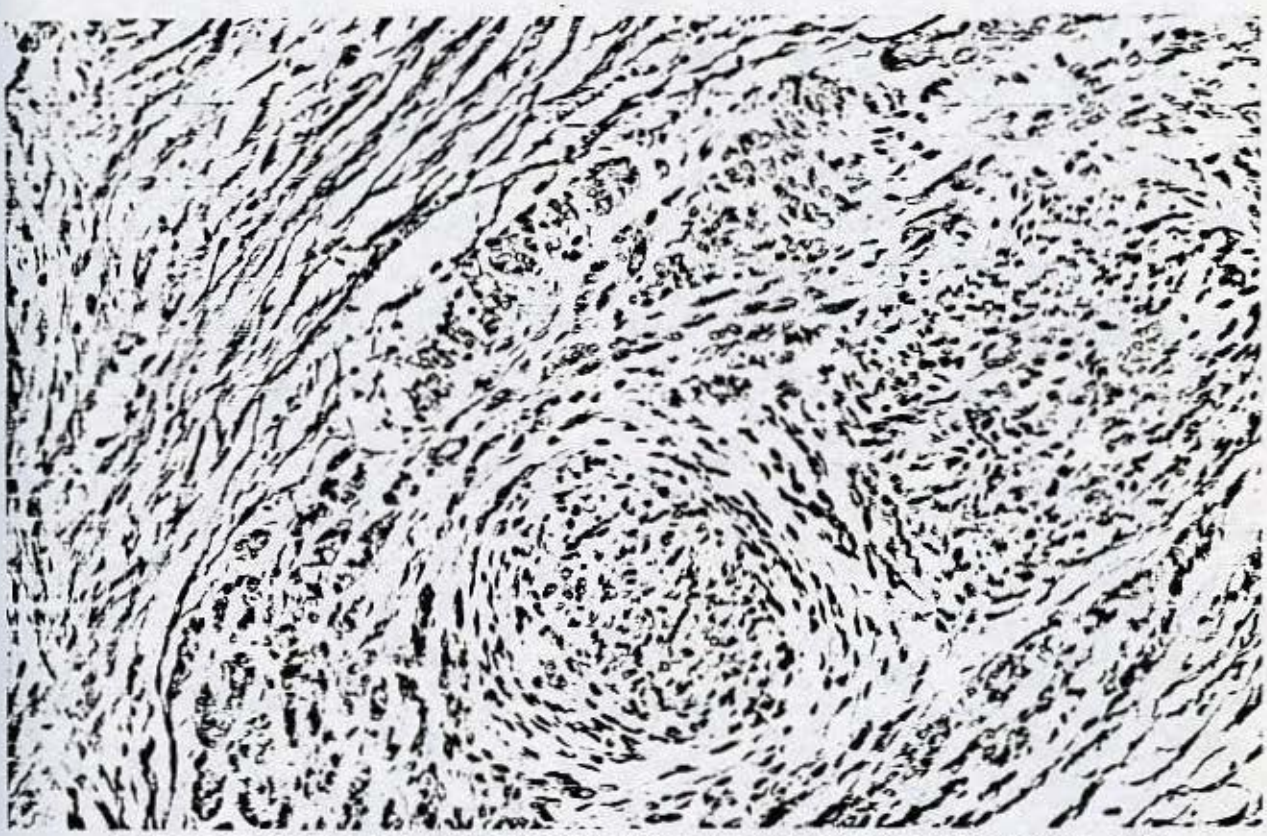

Figure 17. Terminal duct adenocarcinoma showing invasion of small nerves. Hematoxylin and eosin. ×180.

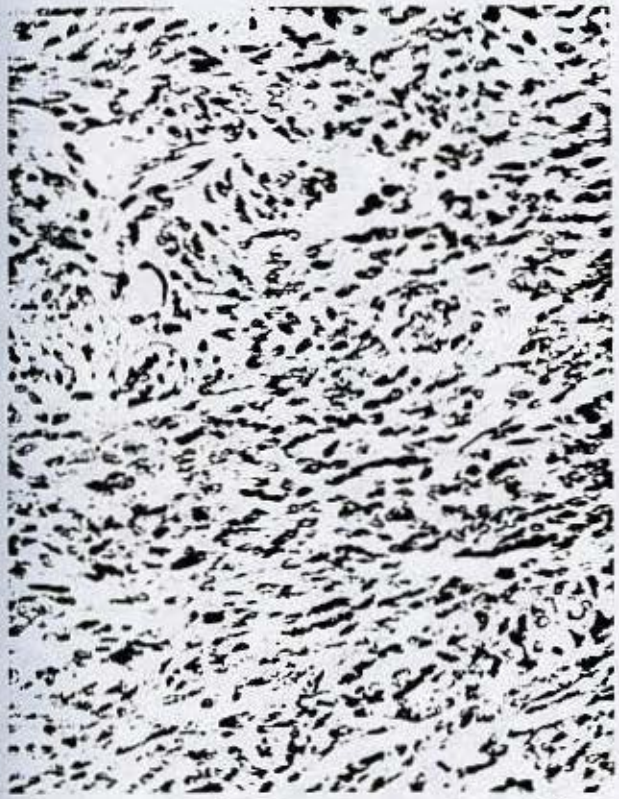

Figure 18. Terminal duct adenocarcinoma. This microscopic field shows the spindle cell elements of the carcinoma. Hematoxylin and eosin. ×185.

REFERENCES

1. Macdonald AM (ed): *Chambers Twentieth Century Dictionary*. Totowa, NJ: Littlefield, Adams, 1974. p 283.
2. Pinkstaff CA: The cytology of salivary glands. *Int Rev Cytol* 63:141–261, 1980.
3. Garrett JR, Emmelin N: Activities of salivary myoepithelial cells: A review. *Med Biol* 57:1–28, 1979.
4. Chisholm DA, Waterhouse JP, Kraucunas E, Sciubba JJ: A quantitative ultrastructural study of the pleomorphic adenoma (mixed tumor) of human minor salivary glands. *Cancer* 34:1631–1641, 1974.
5. Young JA, Van Lennep EW: Morphology and physiology of salivary myoepithelial cells. *Int Rev Physiol* 12:105–125, 1977.
6. Sciubba JJ, Bannon RB: Myoepithelioma of salivary glands: Report of 23 cases. *Cancer* 49:562–572, 1982.
7. Tamarin A: Myoepithelium of the rat submaxillary gland. *J Ultrastruct Res* 16:320–338, 1966.
8. Tandler B, Denning CR, Mandel ID, Kutscher AH: Ultrastructure of human labial salivary glands. III. Myoepithelium and ducts. *J Morphol* 130:227–246, 1970.
9. Franke WW, Schmid E, Freudenstein C, Applhans B, Osborn M, Weber K, Keenan TW: Intermediate-sized filament of the prekeratin type in myoepithelial cells. *J Cell Biol* 84:633–654, 1980.
10. Franke WW, Appelhans B, Schmid E, Freudenstein C, Osborn M, Weber K: Identification and characterization of epithelial cells in mammalian tissues by immunofluorescence microscopy using antibodies to prekeratin. *Differentiation* 15:7–25, 1979.
11. Caselitz J, Löning T, Staquet MJ, Seifert G, Thivolet J:

Immunocytochemical demonstration of filamentous structures in the parotid gland. Occurrence of keratin and actin in normal and tumoral parotid gland with special respect to the myoepithelial cells. *J Cancer Res Clin Oncol* 100:59–68, 1981.
12. Drenckhahn D, Groschel-Stewart U, Unsicker K: Immunofluorescence—microscopic demonstration of myosin and actin in salivary glands and exocrin pancreas of the rat. *Cell Tissue Res* 183:273–279, 1977.
13. Caselitz J, Osborn M, Seifert G, Weber K: Intermediate-sized filaments proteins (prekeratin, vimentin, desmin) in the normal parotid gland and parotid gland tumours. *Virchows Arch [Pathol Anat]* 393:273–286, 1981.
14. Schlegel R, Banks-Schlegal S, Pinkus GS: Immunohistochemical localization of keratin in normal human tissues. *Lab Invest* 42:91–96, 1980.
15. Batsakis JG: Salivary gland neoplasia: An outcome of modified morphogenesis and cytodifferentiation. *Oral Surg* 49:229–232, 1980.
16. Regezi JA, Batsakis JG: Histogenesis of salivary gland neoplasms. *Otolaryngol Clin North Am* 10:297–307, 1977.
17. Cutler LS, Chaudhry AP: Differentation of myoepithelial cells of the rat submandibular gland in vivo and in vitro: An ultrastructural study. *J Morphol* 140:343–354, 1973.
18. Redman RS, Sweeney LR, McLaughlin ST: Differentiation of myoepithelial cells in the developing rat parotid gland. *Am J Anat* 158:299–320, 1980.
19. Hubner G, Klein HJ, Kleinsasser O, Schiefer HG: Role of myoepithelial cells in the development of salivary gland tumors. *Cancer* 27:1255–1261, 1971.
20. Dardick I, van Nostrand AWP, Phillips MJ: Histogenesis of salivary gland pleomorphic adenoma (mixed tumor) with an evaluation of the role of the myoepithelial cell. *Hum Pathol* 13:62–75, 1982.
21. Nesland JM, Olafsson J, Sobrinho-Simoes M: Plasmacytoid myoepithelioma of the palate. *J Oral Pathol* 10:14–21, 1981.
22. Buchner A, David R, Hansen LS: "Hyaline cells" in pleomorphic adenoma of salivary gland origin. *Oral Surg* 52:506–512, 1981.
23. Lomax-Smith JD, Azzopardi JG: The hyaline cell: A distinctive feature of "mixed" salivary tumors. *Histopathology* 2:77–92, 1978.
24. Warner TF, Seo IS: Aggregates of cytofilaments as the cause of the appearance of hyaline tumor cells. *Ultrastructural Pathology* 1:395–401, 1980.
25. Batsakis JG: Clear cell tumors of salivary glands. *Ann Otol Rhinol Laryngol* 89:196–197, 1968.
26. Corio RL, Sciubba JJ, Brannon RB, Batsakis JG: Epithelial-myoepithelial carcinoma of intercalated duct origin. *Oral Surg* 53:280–287, 1982.
27. Batsakis JG, Pinkston GR, Luna MA, Byers RM, Sciubba JJ, Tillery GW: Adenocarcinomas of the oral cavity: A clinicopathologic study of terminal duct carcinomas. *J Laryngol Otol*, to be published.
28. Varela-Duran J, Diaz-Flores L, Varela-Nunez R: Ultrastructure of chondroid syringoma. Role of the myoepithelial cell in the development of the mixed tumor of the skin and soft tissues. *Cancer* 44:148–156, 1979.
29. Azzopardi JG, Smith OD: Salivary gland tumors and their mucins. *Journal Pathology and Bacteriology* 7:131–140. 1959.
30. Takeuchi J, Sobue M, Yodhida M, Esaki T, Katoh Y: Pleomorphic adenoma of the salivary gland. With special reference to histochemical and electron microscopic studies and biochemical analysis of glycosaminoglycans in vivo and in vitro. *Cancer* 36:1771–1789, 1975.
31. Shirasuna K, Sato M, Miyazaki T: A myeopithelial cell line established from a human pleomorphic adenoma arising in minor salivary gland. *Cancer* 45:297–305, 1980.
32. Sciubba JJ, Goldstein BH: Myoepithelioma. Review of the literature and report of a case with ultrastructural confirmation. *Oral Surg* 42:328–338, 1976.
33. Chaudhry AP, Satchidanand S, Peer R, Cutler LS: Myoepithelial cell adenoma of the parotid gland: A light and ultrastructural study. *Cancer* 49:288–293, 1982.

Salivary epithelial-myoepithelial carcinomas of intercalated ducts: A clinical, electron microscopic, and immunocytochemical study

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The salivary epithelial-myoepithelial carcinoma of intercalated duct origin is a distinctive, biologically low-grade carcinoma with a predilection for the parotid gland. Nine examples from the M.D. Anderson Hospital in Houston, Texas, bring the number of published cases to 33. Immunocytochemical (S-100 protein, myosin, and keratin) and electron-optic studies strongly support an active myoepithelial cell participation in the histogenesis of these carcinomas.
(ORAL SURG. ORAL MED. ORAL PATHOL. 59:482-490, 1985)

Neoplasms with a prominent or preponderant clear cell composition have generally been placed under the rubric of "clear cell tumor," but such a descriptive designation does little justice to the different types of cells that may be involved or convey reasons for the light-optic appearance of the cells[1,2]

In epithelial lesions, cytoplasmic clarity is a property occasioned by several mechanisms, such as sparsity of organelles, storage or accumulation of cytoplasmic contents (glycogen, mucins, lipids, clear secretory granules), or an artifactual clearing related to the processing of tissues for histologic examination.

One of the most distinctive salivary gland neoplasms with a clear cell component is the epithelial-myoepithelial carcinoma of intercalated ducts—a neoplasm in which the clear cells have been considered to be myoepithelial in origin.[3]

The purpose of this report is twofold: (1) to present immunocytochemical and electron-optic evidence supporting the contention that myoepithelial cells make up a considerable proportion of epithelial-myoepithelial carcinomas and (2) to provide a contemporary clinical and pathologic assessment of the carcinomas.

MATERIAL AND METHODS

Clinical and histopathologic material from nine cases of epithelial-myoepithelial carcinoma of intercalated duct cell origin were obtained from the surgical pathology files of the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston and reviewed. Histologic sections were available in all nine cases and paraffin blocks in eight. All of the neoplasms were studied in multiple sections stained with hematoxylin and eosin (H & E), periodic acid–Schiff (PAS) before and after

Table I. Antibodies used in immunocytochemical studies

Antigen localized	*Antibody and dilution*	*Source*
S-100 protein	Rabbit anti-ox brain S-100 protein, (α and β units), 1:1,000	Dako Corporation Santa Barbara, Calif.
Keratin	Rabbit anti-human epidermal keratin, prediluted by manufacturer	Dako Corporation Santa Barbara, Calif.
Myosin	Rabbit anti-bovine smooth muscle myosin, 1:100	Dr. L. Donner George Washington University, Washington, D.C.
Amylase	Rabbit anti-human salivary amylase, 1:100	Nordic Immunological Laboratories, El Toro, Calif.

diastase digestion, Meyer's mucicarmine, alcian blue, and periodic acid–methenamine sliver (PAMS).

Material for electron microscopic study was available in three cases. Specimens had been fixed in 2.0% glutaraldehyde in phosphate buffer, postfixed in 1.0% osmium tetroxide in S-collidine buffer, and embedded in Epon. Thin sections were stained with uranyl acetate and lead citrate.

Immunohistochemical studies were carried out on formalin-fixed, paraffin-embedded tissue sections by the avidin-biotin peroxidase complex (ABC) technique as described by Hsu and colleagues.[4] In order to enhance the intensity of the immunoreaction, the tissue sections were treated with 0.1% trypsin* and 0.1% calcium chloride in distilled water, pH 7.8, at 37° C for 20 minutes before they were incubated with the primary antibodies. All primary antibodies used are listed in Table I, together with their sources and working dilutions. The site of the immunoreaction was visualized, with 3-amino-9-ethylcarbazole as the chromogen. The number of positive cells for each antigen was scored semiquantitatively an a 1+ to 3+ scale. The specificity of the immunoreaction was verified by the use of known positive control tissues (sections of melanoma for S-100 protein, skin for keratin, parotid gland for amylase, and blood vessel wall for smooth-muscle myosin). Sections in which normal rabbit serum was substituted for the primary antibodies constituted the negative controls.

*Sigma Chemical Company, St. Louis, Mo.

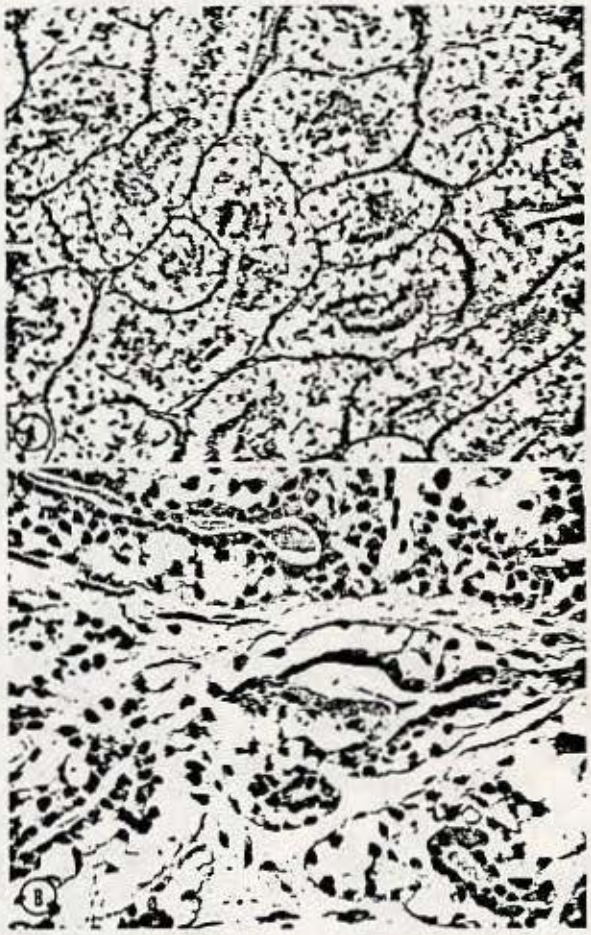

Fig. 1. Biphasic pattern of epithelial-myoepithelial carcinoma of intercalated ducts. (Hematoxylin and eosin stain. Original magnification: A, ×60; B ×240.)

PATHOLOGIC STUDIES

Gross findings

The neoplasms ranged from 2 to 8 cm in greatest dimension. Most of the primary untreated neoplasms appeared as single, well-circumscribed, firm, lobulated, white masses. Two, however, had irregular margins and infiltrated the adjacent tissue. Recurrent neoplasms were lobulated, firm masses with areas of necrosis and irregular, roughened borders.

Light microscopy

The histologic appearance varied not only between neoplasms but also within the same neoplasm. Six tumors were composed of small ducts lined with cuboidal epithelium and surrounded by clear cells overlying an external basement membrane (Fig. 1, *A* and *B*). The cuboidal cells had finely granular, dense eosinophilic cytoplasm and central or basally located, round nuclei. The clear cells were polyhedral

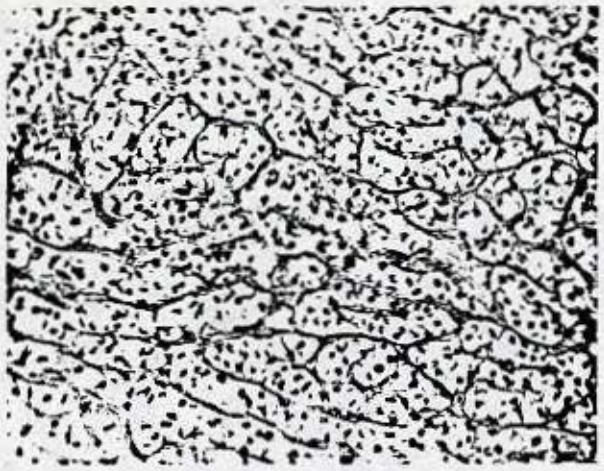

Fig. 2. Epithelial-myoepithelial carcinoma of intercalated ducts in a trabecular growth pattern. (Hematoxylin and eosin, stain. Original magnification, ×150).

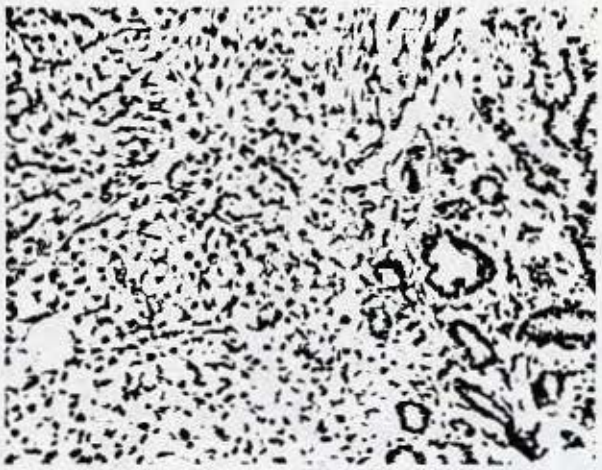

Fig. 3. Transition zone between biphasic and uniphasic areas in epithelial-myoepithelial carcinoma of intercalated ducts. (Hematoxylin and eosin stain. Original magnification, ×60.)

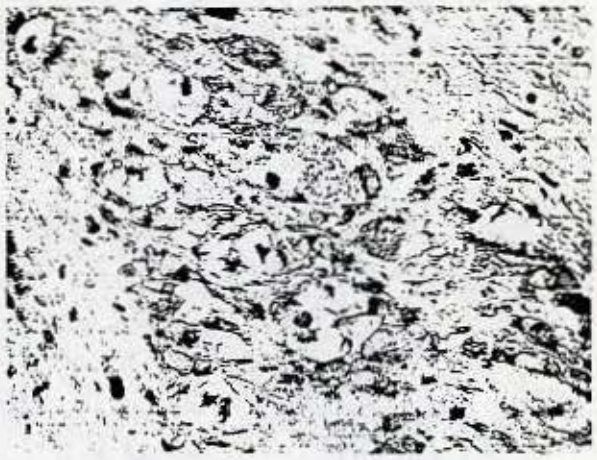

Fig. 4. Case 8. Solid area composed of clear cells showing positive nuclear and cytoplasmic staining for S-100 protein. (ABC stain. Original magnification, ×250).

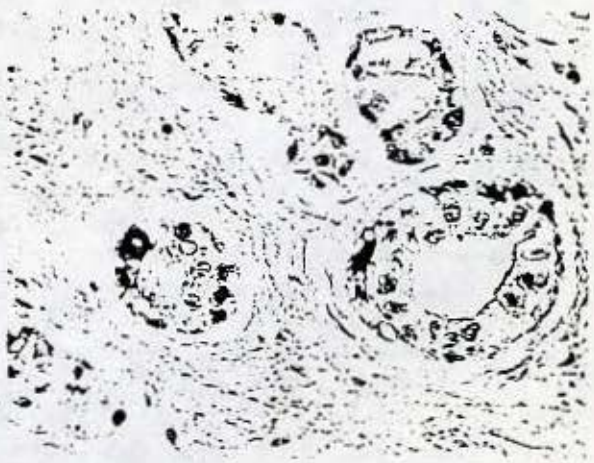

Fig. 5. Case 7. Photomicrograph showing peripheral clear cells positive for S-100 protein. Note that the ductal cells are negative. (ABC stain. Original magnification, ×250.)

with well-defined cell borders and slightly eccentric, vesicular nuclei. Some ductal lumina contained eosinophilic secretory material. In three tumors (cases 3, 6, and 8), the biphasic character of the neoplasm was less apparent. Two of these were composed almost exclusively of clear cells arranged in solid groups separated by fibroconnective tissue. One had a trabecular arrangement of tumor cells that were separated by dense, hyaline, basement-membrane-like material which stained strongly positive with PAS and PAMS stains (Fig. 2). In each of these three neoplasms, there was a transition between solid areas and areas showing biphasic patterns (Fig. 3). Mitotic figures were rare.

Stains demonstrated that the cytoplasm of the clear cells was PAS-positive and diastase-soluble, indicating the presence of glycogen. Intracytoplasmic mucin was not present in either the clear or the ductal cells. On occasion, however, the ductal lumina contained mucicarminophilic and alcian-blue-positive material.

Immunohistochemistry

All eight neoplasms on which immunohistochemical studies were performed showed positive immunoreactive cells for S-100 protein. Typically, the staining occurred in both the nuclei and the cytoplasm of the clear cells. In those that had a preponderantly solid pattern composed almost exclusively of clear cells, the reaction tended to be diffuse (Fig. 4), while

Fig. 6. Case 9. Immunoperoxidase preparation for keratin demonstrating strong immunoreactivity of ductal cells. (ABC stain. Original magnification, ×120.)

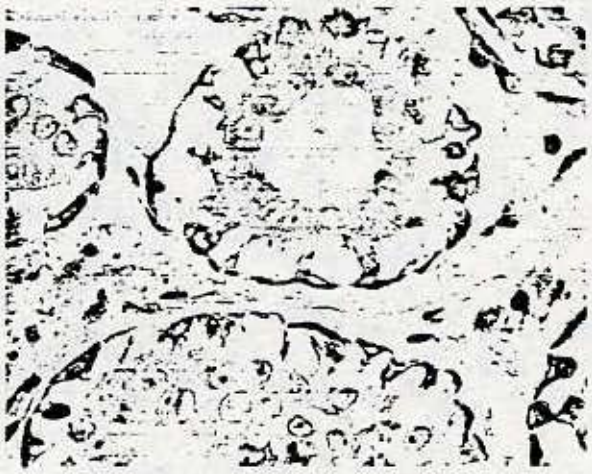

Fig. 7. Case 9. Immunohistochemistry preparation for myosin. The staining is limited to the peripheral clear cells, especially in the portions adjacent to the basement membrane. (ABC stain. Original magnification, ×250).

the reaction was limited to peripheral clear cells surrounding the ductal cells in the biphasic areas (Fig. 5).

Immunoreactivity for keratin was manifested in seven neoplasms. All seven had strong coloring of ductal cells (Fig. 6). A coloring of the clear cells occurred in only five neoplasms, and the reaction was usually weak and focal. The only neoplasm that did not show any immunoreactivity for keratin (Case 8) had a solid pattern and was composed almost exclusively of clear cells.

Three neoplasms (Cases 4, 7, and 9) gave a positive immunoreaction for myosin. The coloring occurred only in the peripherally located clear cells and was most intense in the areas adjacent to the basement membrane (Fig. 7).

Four neoplasms had focal areas of immunoreactivity for amylase. The staining occurred only in the ductal cells and tended to be stronger toward the apex of the cells (Fig. 8). Positive staining for amylase was also observed in secretory material present in the lumina of some ducts. Clear cells were invariably negative for this antibody.

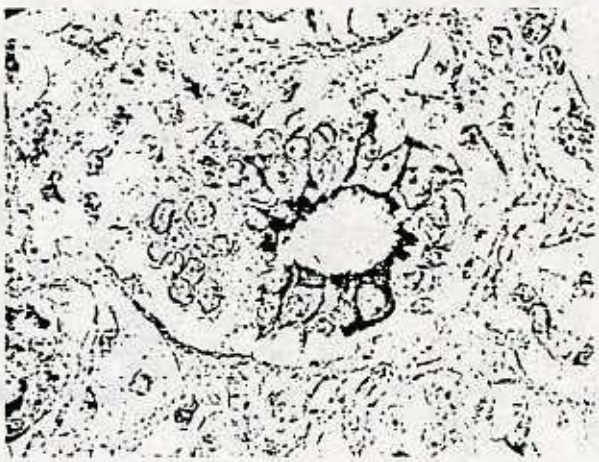

Fig. 8. Case 7. Ductal cells showing positive staining for amylase. (ABC stain. Original magnification, ×350.)

Electron microscopy

Two of the three tumors studied ultrastructurally were among the six that displayed a prominent biphasic pattern on light microscopy (Cases 2 and 4). A corresponding area was identified in semithin sections of Case 2, and Fig. 9 shows the full thickness of the wall of a ductal structure with the two component cell types. The cells bordering the lumen were more or less cuboidal, with an irregular array of atypical microvilli, and many similar peripheral projections protruded into slender clefts between adjacent cells. The round nuclei had evenly dispersed chromatin and inconspicuous nucleoli. The organelles included a moderate number of mitochondria, varying quantities of granular endoplasmic reticulum forming dilated cisternae, and a prominent Golgi complex. A striking feature was the presence of many spherical, membrane-limited dense granules, up to 1 μm in diameter, concentrated within the atypical cytoplasm.

The second cell type typically formed a single layer peripheral to the granule-containing cells, immediately within the basal lamina. These cells and their nuclei were more flattened, and they contained electron-lucent or finely granular lakes of glycogen. A band of microfilaments with interspersed densities, typical of smooth-muscle myofilaments, was

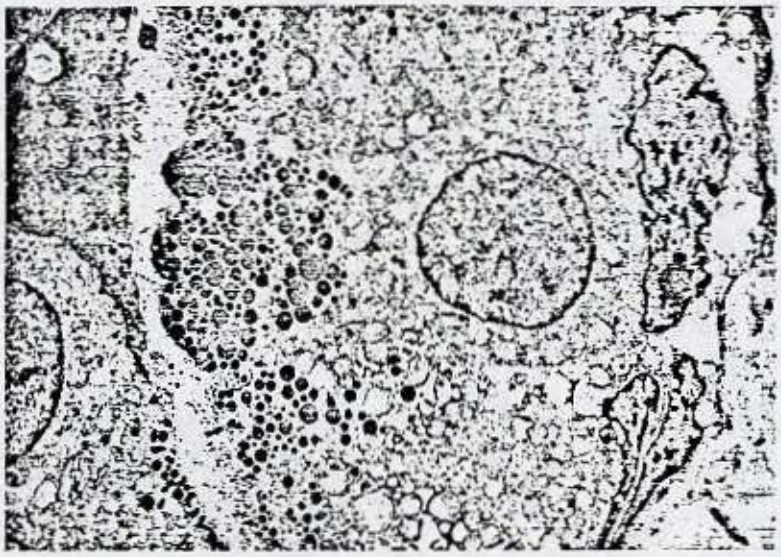

Fig. 9. Case 2. The arrangement and fine structure of the two cell types in this biphasic carcinoma. The inner cuboidal cells contain many large, dense, secretory granules, and an irregular array of microvilli protrudes into a slender lumen. A single layer of vacuolated flattened cells makes up the basal layer. (Original magnification, ×4,000).

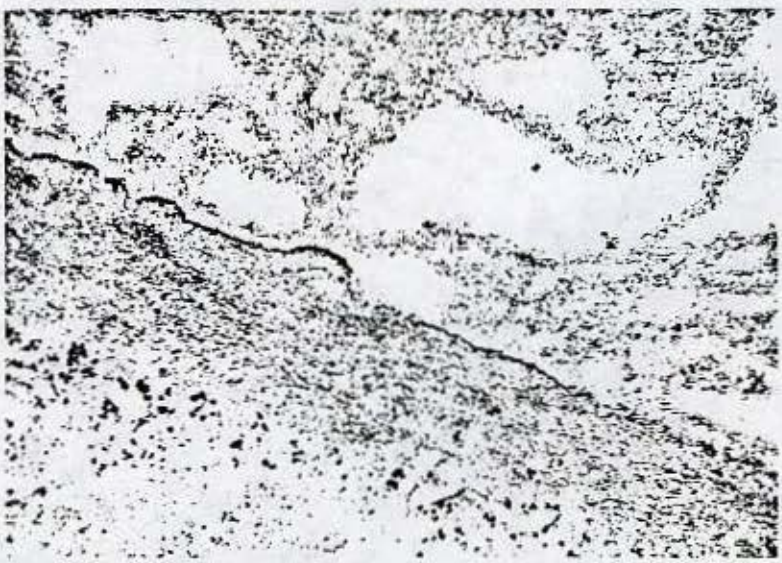

Fig. 10. A detail of the base of the biphasic epithelium from the same tumor as that depicted in Fig. 9, showing particulate glycogen, a slender subplasmalemmal band of smooth-muscle myofilaments, and replication of the basal lamina. Original magnification, ×69,000..)

located close to the outer plasma membrane (Fig. 10) and subplasmalemmal dense plaques were common. There was a striking degree of replication of the external lamina.

A sharp distinction between the two cell types was not always apparent, and some cuboidal cells with microvilli that were lining lumina contained few or no granules but did have a layer of myofilaments in the basal cytoplasm and rested on an external lamina. In areas of the biphasic tumors where the cells appeared by light microscopy to form solid sheets, small lumina with at most a few abortive microvilli were common (Fig. 11, Case 4). Cells within these solid groups did not otherwise show any polarity. They contained abundant glycogen, diffuse zones of filaments that were focally condensed in the manner of smooth-muscle myofilaments, prominent desmosomes with short tonofilament bundles, and

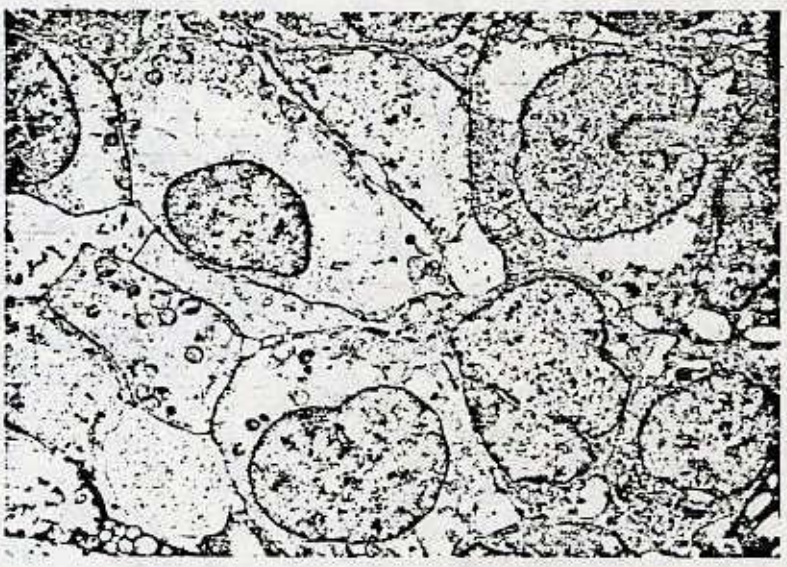

Fig. 11. Case 4. In a solid grouping of cells from a preponderantly biphasic carcinoma, small lumina with sparse microvilli can be detected at the ultrastructural level. Much of the cytoplasm appears clear because of large amounts of glycogen. Original magnification, ×4,200.)

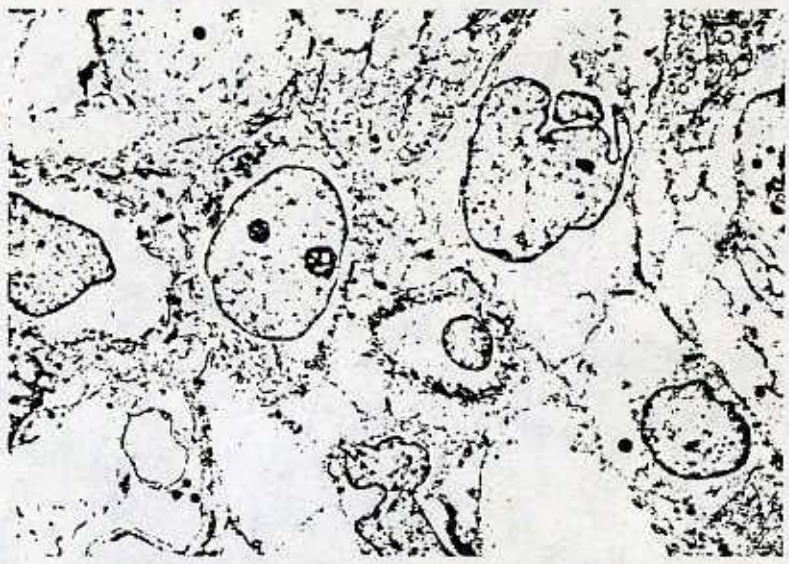

Fig. 12. Case 3. Many of the glycogen-rich cells in this preponderantly uniphasic (solid) carcinoma contained prominent bundles of prekeratin filaments. (Original magnification, ×4,200).

small numbers of round, dense bodies in occasional cells. Marked duplication of the basal lamina was again evident.

A more or less similar appearance was seen in Case 3, one of the carcinomas that showed limited evidence of a biphasic architecture by light microscopy, but the numerous desmosomes were accompanied in some cells by conspicuous bundles of tonofilaments (Fig. 12). A number of the cells with prominent tonofilaments were situated at the periphery of the tumor cell groups, adjacent to the collagenous stroma. A basal lamina was commonly, but not invariably, present, and it was not multilayered in this tumor. Occasional cells contained a thin band of myofilaments in the peripheral cytoplasm and, unlike the other two tumors studied with the electron microscope, the myofilaments were not confined to the outermost cells of a group and, therefore, did not always lie alongside a basal lamina. Organelles were sparse, and there were only scattered clusters of round, dense bodies. A few lipid droplets were present in most of the cells.

Table II. Epithelial-myoepithelial carcinomas of intercalaed duct origin

No.	*Age*	*Sex*	*Location*	*Size (cm)*	*Invasion*	*Treatment*	*Recurrence*	*Follow-up*
1	63	F	Rt. parotid	5 × 4 × 5	Nerves and soft tissue	Total parotidectomy, mandibulectomy, 5,535 rads	One, 1 yr	NED, 7 yr
2	54	M	Lt. antrum	3 × 3 × 2	Ethmoid and sinus wall	Maxillectomy	None	NED, 6 yr
3	77	F	Lt. parotid	3 × 2 × 3	None	Total parotidectomy, 5,000 rads	None	NED, 9 yr
4	72	F	Lt. parotid	5 × 4 × 5	Facial nerve	Superficial parotidectomy, total parotidectomy, 5,000 rads	Two, 3 and 4 yr	NED, 13 yr
5	72	M	Rt. parotid	8 × 6 × 5	Bone and soft tissue	Superficial parotidectomy, total parotidectomy, mandibulectomy, and neck dissection	Two, 1 and 2 yr	DOD, 7 yr
6	52	F	Lt. parotid	3 × 2 × 1.5	Nerves	Total parotidectomy and neck dissection, 6,000 rads	None	DOC, NED, 9 yr
7	57	M	Lt. parotid	2 × 1.5 × 1	Soft tissues	Superficial parotidectomy	None	NED, 11 yr
8	63	F	Rt. parotid	5 × 4 × 3	Soft tissues	Superficial parotidectomy, 6,000 rads	One, 2 yr	DOC, NED, 3 yr
9	68	F	Lt. parotid	Unknown	Soft tissues	Superficial parotidectomy, local excision, and neck dissection	Three, 6, 7, and 8 yr	LWD, 8 yr

NED = No evidence of disease; DOD = died of disease; DOC = died of other causes; LWD = living with disease.

Clinical findings

The age of the patients ranged from 52 to 77 years (mean, 64.2 years). Six patients were women and three were men. Eight neoplasms occurred in the parotid gland (five in the left and three in the right), and one was located in the left maxillary sinus. All patients had swelling in the parotid area. Two patients complained of pain. Nasal obstruction and facial deformity were the major complaints of the patient with the maxillary neoplasm.

Table II summarizes selected clinical and pathologic data on the M. D. Anderson Hospital patients. Four patients were treated by surgical excision alone (Cases 3, 5, 7, and 9). Surgical resection of the tumor followed by irradiation was the initial treatment in two patients (Cases 3 and 6). The remaining three patients (Case 1, 4, and 8) were initially treated by surgical resection of the tumor and received irradiation when the tumor recurred. The radiation dosages varied from 5,000 to 6,000 rads (tumor dose) delivered over a 5- to 6-week period.

Follow-up information was obtained on all the patients. Four had no evidence of recurrence over a 6- to 11-year period. Five patients had recurrence of tumor between 1 and 6 years after initial treatment. Two of these patients had two recurrences each, and one patient had three recurrences. At the time of preparation of this publication, seven patients are alive. Six remain free of disease, and one has tumor involving the left side of the face, neck, and the base of the skull. Two patients are dead. One, who died of an unrelated cause, was free of disease. In the other cervical lymph node, neck soft tissue, and lung metastases developed.

DISCUSSION

The immunocytochemical and electron-optic findings in this study of epithelial-myoepithelial carcinomas of intercalated ducts provide additional objective evidence for the contentions that (1) the clear cells of the carcinomas manifest myoepithelial differentiation, (2) the myoepithelial-differentiated cells share intermediate (cytokeratin) filament proteins with the intercalated duct cells, and (3) the clear cells store glycogen but do not produce or store amylase.

The selective coloring of the clear cells in the immunoreactions for myosin and S-100 protein is in agreement with the phenotypic expressions and functional properties attributed to myoepithelial.[5-7] When applied to salivary tissues and salivary tumors, S-100 protein has been shown to be a selective marker of myoepithelial cells and their lineage.[8,9] The smooth-muscle myosin antibody used in this study is a protein distinct from skeletal, cardiac, or nonmyogenous myosins and is considered to be a very reliable marker of smooth muscle.[10,11]

In the three carcinomas studied with the electron microscope it was possible to compare the biphasic pattern, which constitutes the characteristic histologic feature of the epithelial-myoepithelial carcinomas, with the solid areas of clear cells that form portions of the biphasic tumors and the bulk of the predominantly solid variants. There was good agreement between the ultrastructural and immunocytochemical results. The cells forming the biphasic ductal structures display two clearly distinct lines of differentiation. The inner cells have microvilli and other epithelial features, and they contain zymogen granules, often in considerable numbers. The outer cells form a single layer immediately within the external lamina, typical of myoepithelial cells, and they contain abundant glycogen and a peripheral band of smooth-muscle myofilaments. In some of the ducts, transitional forms displaying combinations of features of the two cell types are present, and comparable cells form the solid areas of the tumors, in both the minority component of a mainly biphasic carcinoma and the dominant pattern of a carcinoma with scanty biphasic composition. Similar cells in pleomorphic adenomas have been called modified myoepithelial cells.[5] They frequently contain many diffuse filaments, with foci of condensation to typical smooth-muscle myofilaments, particularly at the cell periphery. The extensive glycogen is reminiscent of the myoepithelial-type cells of the biphasic pattern, while the many small lumina throughout the solid areas are a facet of the epithelial influence. In both patterns the basal lamina can display elaborate replication. The biphasic pattern thus shows divergent differentiation into ductal and myoepithelial cells, while the solid areas of the tumors are composed of cells that manifest, to varying degrees, features of both cell types.

According to our observations, the epithelial-myoepithelial carcinoma of intercalated ducts joins pleomorphic adenoma and adenoid cystic carcinoma as a salivary neoplasm in which immunocytochemistry and electron microscopy indicate an integral constitutive role for the myoepithelial cell in pathogenesis. Histogenetically, our findings also link the intercalated duct cell with the myoepithelial cell through their cytokeratins. Bidirectional differentiation from a single stem cell is thereby suggested.[12,13]

Table III. Salivary epithelial-myoepithelial carcinoma of intercalated duct origin: summary of cases (literature and M. D. Anderson Hospital)

Sex of patients	Females, 22; males,	11
Mean age at diagnosis (yr)	62 (range, 31-89)	
Site of primary	Parotid gland:	27
	Submandibular gland:	4
	Cheek:	1
	Maxillary antrum:	1
Size of neoplasm (range in cm)	1.8-8.0	
Patients with recurrences	13 (39%)	
Patient deaths attributed to neoplasm	2 (6%)	

From a clinical standpoint, our experience differs little from that given in the review by Corio and co-workers.[3] The carcinoma manifests a female preponderance, a predilection for major salivary glands, especially the parotid gland, and a low-grade biologic course marked by recurrences and local invasiveness. Table III presents a summary of thirty-three cases of this distinctive salivary carcinoma, including the nine cases in this report and those reviewed by Corio and associates.[3]

REFERENCES

1. Batsakis JG: Clear cell tumors of salivary glands. Ann Otol **89:** 196-197, 1980.
2. Seifert G, Donath K: Über das Vorkommen sog heller Zellen in Speicheldrusentumoren: Ultrastruktur und Differentialdiagnose. Z Krebsforsch **91:** 165-182, 1978.
3. Corio RL, Sciubba JJ, Brannon RB, Batsakis JG: Epithelial-myoepithelial carcinoma of intercalated duct origin. Oral Surg Oral Med Oral Pathol **53:** 280-287, 1982.
4. Hsu S-M, Raine L, Fanger H: Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: a comparison between ABC and unlabeled antibody (PAP) procedures. J Histochem Cytochem **29:** 577-580, 1981.
5. Erlandson RA, Cardon-Cardo C, Higgins PJ: Histogenesis of benign pleomorphic adenoma (mixed tumor) of the major salivary glands: an ultrastructural and immunohistochemical study. Am J Surg Pathol **8:** 803-820, 1984.
6. Young JA, Van Lennep EW: The morphology of salivary glands. London, 1978, Academic Press, Inc., pp. 93-99.
7. Saku T, Okabe H, Yagi Y, Sato E, Tsuda, N: A comparative study on the immunolocalization of keratin and myosin in salivary gland tumors. Acta Pathol Jpn **34:** 1031-1040, 1984.
8. Hara K, Ito M, Takeuchi J, Iijima S, Endo T, Hidaka H: Distribution of S-100 protein in normal salivary glands and salivary gland tumors. Virchows Arch Pathol (A) **401:** 237-249, 1983.

9. Kahn HJ, Marks A, Thom H, Baumal R: Role of antibody to S-100 protein in diagnostic pathology. Am J Clin Pathol **79:** 341-347, 1983.
10. Donner L, de Lanerolle P, Costa J: Immunoreactivity of paraffin-embedded normal tissues and mesenchymal tumors for smooth muscle myosin. Am J Clin Pathol **80:** 677-681, 1983.
11. de Lanerolle P, Stull JT: Myosin phosphorylation during contraction and relaxation of tracheal smooth muscle. J Biol Chem **255:** 9993-10000, 1980.
12. Regezi JA, Batsakis JG: Histogenesis of salivary gland neoplasms. Otolaryngol Clin North Am **10:** 297-307, 1977.
13 Batsakis JC: Salivary gland neoplasia: an outcome of modified morphogenesis and cytodifferentiation. ORAL SURG ORAL MED ORAL PATHOL **49:** 229-232, 1980.

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Case 5. Auditory canal, nodular fasciitis

Most patients give a history of a rapidly growing lesion or of a mass present for a short duration. Pain, tenderness occur in about half of the cases.

The lesions are only rarely multiple and are most often seen in young adults (20-30 years).

The upper extremities (particularly volar forearms) are the most common sites of involvement, with the trunk next in frequency. Head and neck presentation is rare in adults but is the most common site of involvement in children.

Nodular fasciitis exists in three anatomic forms: (1) subcutaneous, (2) intramuscular, (3) fascial. The first is the most commonly encountered.

The lesional fibroblasts are usually arranged in short irregular bundles and fascicles without mature collagen. There is usually an abundant ground substance and this accounts for the loosely textured pattern of nodular fasciitis. The fibroblasts vary little in their size and shape. Mitoses may be fairly numerous, but are never atypical. All in all, there is a tissue culture aura to the proliferating cells. Extravasated red blood cells may be numerous.

With aging of the lesion, maturation occurs in the form of hyaline fibrosis.

Nearly all of the lesions are cured by local excision. Recurrence is rare. Spontaneous regression has been seen.

The Table presents the sites of involvement of head and neck nodular fasciitis.

Shimizu, S., Hashimato, H. and Enjoi, M.: Nodular fasciitis: An analysis of 250 patients. Pathology 16:161-166, 1984.

Allen, P.W.: Nodular fasciitis. Pathology 4:9-26, 1972.

Dahl, I., Jarlstedt, J.: Nodular fasciitis in the head and neck. A clinicopathological study of 18 cases. Acta Otolaryngol. 90:152-159, 1980.

Meister, P., Buckmann, F.W., and Konrad, E.: Extent and level of fascial involvement in 100 cases with nodular fasciitis. Virchows Arch. Path. Anat. (A). 380:177-185, 1979.

Nodular Fasciitis in the Head and Neck

Site	Number
Facial Soft Tissues	97
Neck	64
Forehead	21
Eyelid	15
Scalp	14
Parotid Sheath	9
Head and Neck (not specified)	16

Case 6. Myxoid liposarcoma, neck

Hypopharyngeal lipomatous tumors are invariably more or less pedunculated. Their diameter varies from 2 to 4 cm and they may be up to 20 cm in length. In about one-quarter of cases, the pedunculated hypopharyngeal fibrolipoma is multiple. Tumor location varies; lateral hypopharyngeal wall, the pyriform fossa, the aryteno-epiglottic folds, the region of the arytenoids, post-cricoid region and proximal esophagus from the level of the crico-pharyngeal sphincter.

Clinical presentation is usually in the fourth decade and men exceed women in a ratio of 4:1.

Many go undiagnosed for years. Some patients may experience some slight dysphagia with minor aspiration on swallowing, or a sensation of a lump in the throat. Periodic hoarseness may occur and transient respiratory distress can be noted. Clinical presentation may be dramatic with the mass coming up into the pharynx and mouth. Laryngeal impaction may give rise to acute upper airway obstruction and rarely sudden death.

Malignant transformation, if it occurs, must be rare. By 1985, eight cases of laryngeal liposarcoma had been reported in the English language literature.

Like the seminar case, the tumors are usually histologically low-grade liposarcomas. The included reprint entails a review of lipomatous tumors of the head and neck.

Laurent, C., Lindholm, C.E., and Nordlinder, H.: Benign pedunculated tumours of the hypopharynx. Three case reports, one with late malignant transformation, ORL. 47:17-21, 1985.

Allsbrook, W.C., Harmon, J.D., Chongchitnant, N., and Erwin, S.: Liposarcoma of the larynx. Arch Pathol. Lab. Med. 109:294-296, 1985.

Batsakis, J.G., Regezi, J.A., and Rice, D.H.: The pathology of head and neck tumours: fibroadipose tissue and skeletal muscle, part 8. Head and Neck Surg. 3:145-168, 1980.

THE PATHOLOGY OF HEAD AND NECK TUMORS: FIBROADIPOSE TISSUE AND SKELETAL MUSCLE, PART 8

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Abstract: Benign and malignant tumors originating from mesenchymal cells destined to become lipoblasts and myoblasts affect the head and neck with contrasting frequencies. Lipomas and especially liposarcomas are unusual lesions above the clavicles but when found there behave in a biologic manner identical to that of their counterparts at other anatomic sites. Myogenic tumors, on the other hand, have a predilection for the head and neck, and for rhabdomyosarcomas this predilection is accentuated in childhood. Combination therapy of rhabdomyosarcomas has obviated radical surgery as a method of treatment, and many sites in the head and neck have benefited prognostically by this treatment. Success, however, is dependent on clinical stage of disease, and rhabdomyosarcomas of the nasopharynx, paranasal sinuses, and middle ear remain more resistant to short-term cures because of the extent of the neoplasm. A review of the clinicopathologic aspects of granular-cell tumors and alveolar soft-part sarcomas is also presented because it has been suggested that these tumors have a myogenous origin.

HEAD & NECK SURGERY 3:145–168 1980

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This review considers 2 classes of tumors of the supporting tissue as they affect the head and neck—tumors of lipoblastic tissues and tumors of skeletal muscle or its precursors. The 2 classes represent nearly opposite poles of the incidence spectrum in that lipoblastic tumors are infrequent in the head and neck, whereas tumors of skeletal muscle origin have a definitive predilection for the head and neck, especially in children, as well as for the lower genitourinary tract.

Malignant varieties of the 2 classes do not evolve through a benign precursor lesion, but appear de novo; lipomas do not "degenerate" to liposarcomas, and rhabdomyomas do not evolve into rhabdomyosarcomas. Benign lipogenic tumors far outnumber their malignant counterparts, while the number of rhabdomyosarcomas greatly exceeds the number of rhabdomyomas. Liposarcomas are rare in children, whereas rhabdomyosarcomas comprise the most common soft-tissue malignancy of the head and neck in children.

BENIGN LIPOBLASTIC DISORDERS

Table 1 presents a brief clinicopathologic classification of lipomas, including hibernoma. Note that the noninfiltrating varieties are characterized by their superficial location and encapsulation. The atypical lipoma is often classified as a well-differentiated liposarcoma because of cytologic atypia of some of the lipoblasts. We agree with Evans et al.[1] that in such instances, the site (superficial or deep) of the tumor outweighs cytologic atypia as far as biologic behavior is concerned. In that light, we assume *all* superficial or subcutaneous lipogenic tumors to be biologically benign in terms of their ability to metastasize.

Conventional Lipomas. The conventional lipoma is the tumor most familiar to medical students and patients. It consists of mature fibroadipose tissue

Table 1. A clinicopathologic classification of lipomas

Lipomas	Characteristics
Conventional lipomas	Subcutaneous; well-defined; may be encapsulated
Angiolipomas	
Noninfiltrating	Subcutaneous; sometimes multiple; usually painful; circumscribed; recurrences rare
Infiltrating	Ill-defined; deep-seated; involve muscle, bone, and soft tissues
Other infiltrating lipomas (without vascular component)	
Intermuscular	Probably arise from intermuscular fascial septa
Intramuscular	Originate within muscle bundles
With atypia	
Without atypia	
Spindle-cell lipomas	Usually subcutaneous; usually well-circumscribed; posterior neck and shoulders of older males; benign course; no recurrences
Atypical lipomas	Subcutaneous; well-circumscribed; benign course; no recurrences
Hibernomas	Encapsulated; areas of predilection are neck and interscapular area; majority are subcutaneous

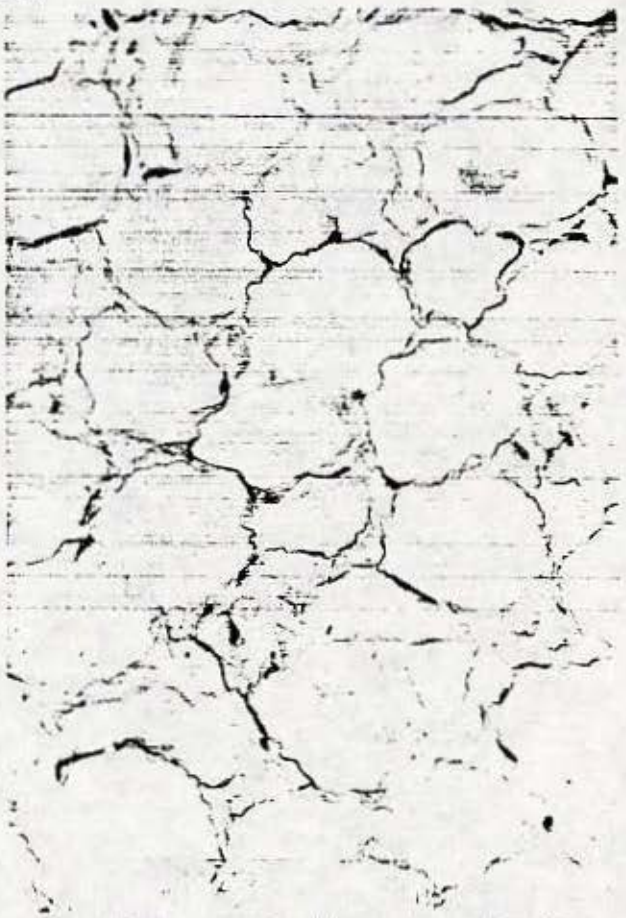

Figure 1. Benign conventional lipoma. Mature fibroadipose cells comprise this tumor. Hematoxylin and eosin, ×140.

with varying degrees of fibrosis. These lipomas are most often solitary and except for cosmetic or obstructive effects are asymptomatic. Unless encapsulated, they may be indistinguishable from herniated normal fat tissue (Fig. 1).

Angiolipomas. Angiolipomas, a variant of lipoma, comprise between 5% and 17% of all lipomas.[2] The angiolipoma exists in 2 biologic forms—noninfiltrating and infiltrating. The former is more common and is usually an encapsulated subcutaneous nodule that may be associated with pain. The infiltrating angiolipoma is more deep-seated and, although histologically benign, can infiltrate bony, muscular, neural, and fibrocollagenous tissues.

Both infiltrating and noninfiltrating forms of angiolipoma contain a lipomatous element having the appearance of normal adipose tissue. The angiomatous component shows different types of mature arteries, veins, and capillaries (Fig. 2).

Other Infiltrating Lipomas Without a Vascular Component. These lipomas exist in 2 forms—the more common intermuscular variety and the intramuscular form.[2] The intermuscular infiltrating lipoma grows in between large muscle bundles and probably arises from intermuscular fascial septa. The tumor is typically large and only secondarily infiltrates the adjacent muscle. The intramuscular lipoma originates between muscle fibers within the muscle bundles themselves and infiltrates and passes through the intermuscular septa. The fibers of muscle entrapped within the tumor growth frequently appear atrophic. Microscopically, both types of tumor are composed of adult adipose tissue.

Spindle-Cell Lipomas. This specific form of lipoma (Fig. 3) may be mistaken for a liposarcoma by the unwary pathologist.[3,4] It occurs chiefly in male patients between 45 and 70 years of age and affects the regions of the shoulders and posterior neck almost exclusively. In most cases the tumor is a dermal or subcutaneous lesion. Most lesions are painless. The tumors are usually well-circumscribed and round or discoid. They rarely exhibit infiltration into underlying muscle.

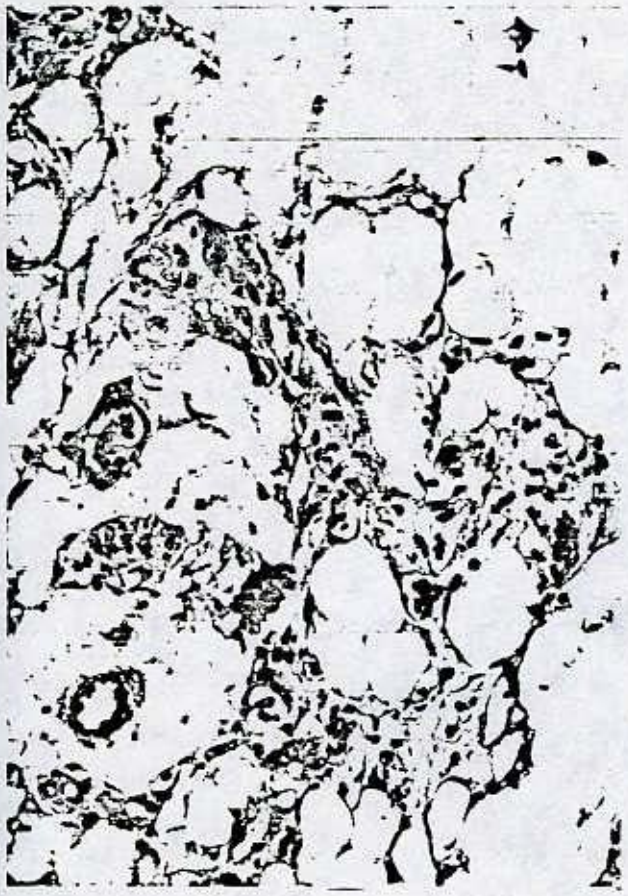

Figure 2. Angiolipoma. The lipomatous tissue contains numerous richly vascularized septa. Hematoxylin and eosin, ×130.

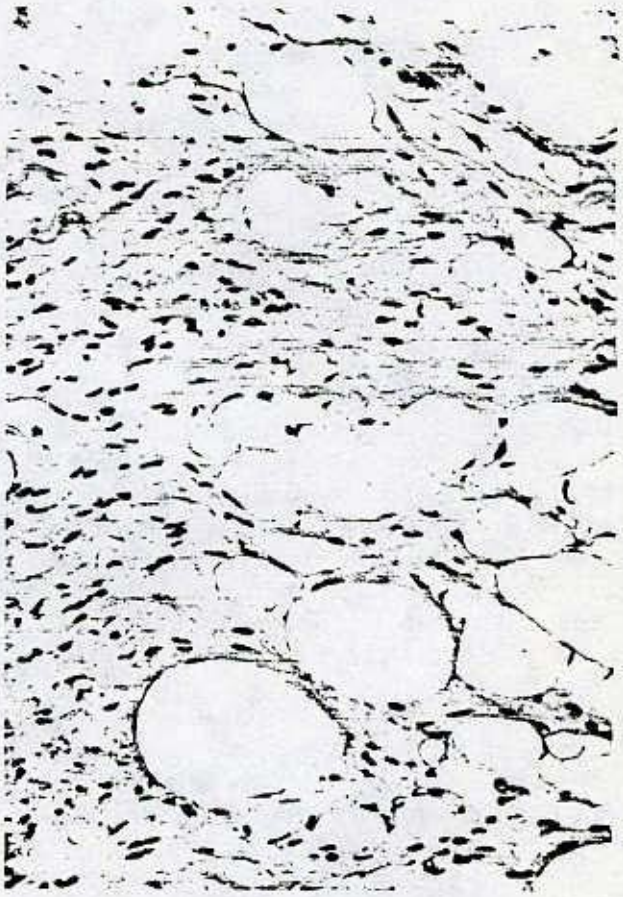

Figure 3. Spindle-cell lipoma. This lipoma contains young fibroblastic tissue with spindled nuclei. Its superficial position, occurrence in the elderly, and typical posterior neck position assist in diagnosis. Hematoxylin and eosin, ×130.

In gross appearance they are firm or gelatinous and yellow or yellow-gray. The size of the tumors varies from 1.0 to 13.0 cm (mean 4.5 cm).

Microscopically, the spindle-cell lipoma consists of a mixture of fat cells and fibroblast-like spindle cells, ultrastructurally similar to fibroblasts, in a matrix with varying amounts of collagen and mucosubstances. The number and distribution of spindle cells vary both within different areas of the same tumor and from tumor to tumor, but the cells are most often arranged haphazardly. The fat cells are univacuolated for the most part. Most of the tumors are relatively avascular except those having a more myxomatous character.

Recurrences are very unusual even when surgical excision has been considered incomplete.

Atypical Lipomas. These are lipogenic tumors whose cytologic atypia exceeds that found in lipomas but which lack other histologic evidence of malignancy.[1] Formerly classed as well-differentiated or grade 1 liposarcomas, their benign behavior has led to their re-evaluation and classification as atypical lipomas. The majority are limited to the subcutaneous tissues, but deep forms (intramuscular) have also been identified.

Lipomatosis. This disorder is characterized by the abnormal deposition of lipomatous tissue.[5] Three different clinical types may be recognized: (*1*) diffuse, congenital lipomatosis, localized mainly to the trunk and not well demarcated from surrounding structures and spreading between muscle fibers; (*2*) symmetrical, diffuse lipomatosis appearing in adult life and primarily localized to the neck but occasionally accompanied by symmetrical lipomatosis in other parts of the body; and (*3*) multiple lipomatosis consisting of usually numerous, small, well-defined, subcutaneous lipomas, mainly localized to the limbs.

The form occurring in the neck may cause such massive swelling as to result in disfigurement and respiratory distress. The tissue accumu-

Figure 4. Gross appearance of a hibernoma of the neck.

lates in large, lobulated masses and may extend between the cervical and upper thoracic muscles. A "horse-collar" cervical appearance is often presented. The cause of this swelling is progressive enlargement of the tumors (this progress may be erratic). There is no characteristic microscopic appearance and, except for some increase in fibrous and vascular tissue, the cells are indistinguishable from those of a lipoma.

Benign Lipoblastoma and Benign Lipoblastomatosis. The lipoblastoma is a benign tumor of fat that occurs exclusively during the years of infancy and, because of its immature cellular appearance, is likely to be confused with a myxoid liposarcoma.

The tumor presents in children younger than 3 years of age and chiefly affects the soft tissue of the upper and lower extremities. Four cases in the Armed Forces Institute of Pathology series of 35 cases occurred in the neck.[6] There are 2 forms of the tumor—circumscribed and diffuse. The former tends to be superficially located and is clinically comparable to a lipoma. The latter is more deeply situated and is analogous to an infantile lipomatosis. In deference to their different locations, the superficial lesion is called benign lipoblastoma and the diffuse lesion, benign lipoblastomatosis.

Microscopically, the 2 forms have an identical histologic appearance. This consists of lobulated immature adipose tissue composed of lipoblasts, a plexiform capillary pattern, and a richly myxoid stroma. The lobular arrangement of the fat cells is characteristic. The lobules are separated by fibrous connective tissue septa or trabeculae. Most of the tumors are well-circumscribed, but some of the deeply seated tumors may exhibit infiltration of muscle in the manner of a diffuse lipomatosis.

The immaturity of the cells may suggest the diagnosis of liposarcoma, but the pathologist should be aided by the fact that liposarcomas are exceedingly rare—or nonexistent—in the age group presenting with lipoblastoma.

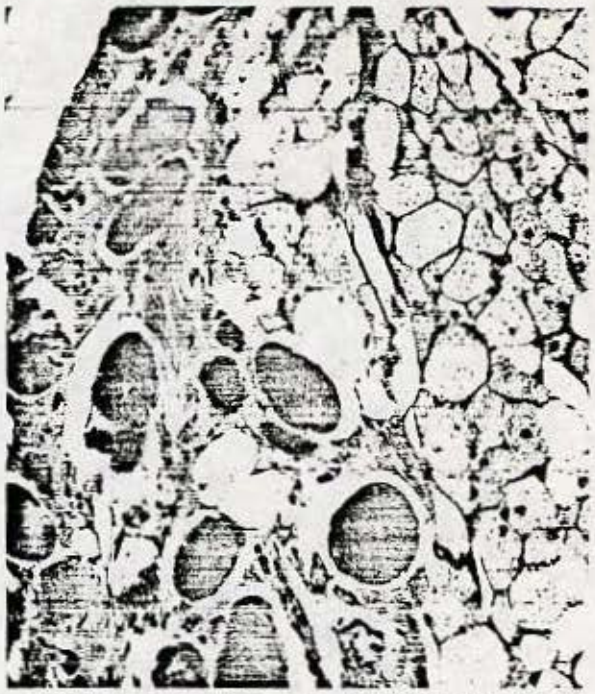

Figure 5. Cells of a hibernoma infiltrating skeletal muscle fibers. Hematoxylin and eosin, ×85.

The tumors follow a benign course with a low rate of recurrence. Recurrences, most often of the deep lipoblastomas, are usually attributable to incomplete surgical removal.

Hibernoma. This tumor represents the neoplastic counterpart of brown fat. It arises from the multivacuolated fat that may be found in select sites in human infants and adults. Whether the multivacuolated fat is truly analogous to the brown fat of hibernating animals or merely a fetal form of white fat remains controversial.

The tumors are usually slow-growing and asymptomatic. Hibernomas are benign tumors; if a malignant hibernoma exists, it has not been reported and it would be difficult, if not impossible, to distinguish it from a round-cell liposarcoma.

According to 2 surveys,[7,8] approximately 12% of the reported hibernomas have occurred in the neck region, but the interscapular area is the preferred site.

Gross examination shows hibernomas to be usually well-encapsulated, vascular, and typically tan to red-brown (Fig. 4). The lobulated mass is firm, freely movable, and nonpainful. The size of the tumors varies from 3 to 19 cm with a mean diameter of 8 cm. Infiltrative growth is not usually a feature, and the tumors usually can be readily separated from the surrounding tissues (Fig. 5).

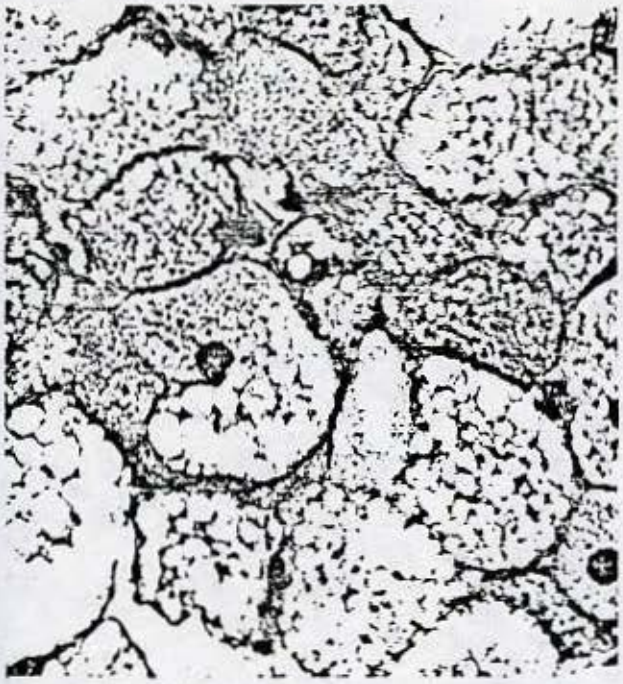

Figure 6. Typical light microscopic appearance of a hibernoma with multivacuolated tumor cells. Hematoxylin and eosin, ×150.

By light microscopic examination, the tumor cells are arranged in distinct lobules with the principal cell being a multivacuolated fat cell (Fig. 6). All stages from lipid-free cells with an eosinophilic granular cytoplasm to multivacuolated cells may be present. The vascularity is prominent and consists of many muscular arteries as well as dilated veins.

Ultrastructurally, the hibernoma appears distinct from the lipoma and very similar to the brown fat of lower animals.[9]

LIPOMAS OF THE UPPER AERODIGESTIVE TRACTS

Statistics concerning the incidence of lipomas of the oral cavity are very likely misleading since we believe many such lipomas are unreported. The recorded incidence varies from 0.2% to 4% of all benign oral tumors.[10] Congenital or infantile forms are rare, and most of the tumors are discovered in middle-aged patients. The predominant locations for these submucosal tumors are the cheek, tongue, floor of the mouth, buccal vestibule, palate, lip, and gingiva, in that order.[10] Nearly all are of the conventional type. Infiltrating lipomas and angiolipomas occasionally present in the oral cavity.

Lipomas of the pharyngeal region may be striking clinical entities and may occur in any

Table 2. Anatomic sites of origin of 50 documented liposarcomas of the head and neck.*

Anatomic site	Number of cases
Neck, pharynx, and parapharyngeal region	23
Cheek	8
Orbit	7
Soft palate	4
Floor of mouth	3
Larynx	3
Lip	1
Mastoid	1
Total	50

**Based on data provided by Saunders et al.,[16] Baden and Newman,[15] Kindblom et al.,[17] and Hudson et al.[18] (excludes sites in skull, scalp, and meninges).*

structure or area of the pharyngeal wall: pharyngoepiglottic, aryepiglottic, and glossoepiglottic folds; the valleculae; the choanal edge (in rare instances); the palatopharyngeal fold or the lateral hypopharyngeal wall; the nasopharyngeal vault; the region of the torus tubarius; and the upper surface of the soft palate.[11] Authors have usually divided these lipomas according to their area of origin: (*1*) tumors originating in the pharynx and hypopharynx, (*2*) retropharyngeal tumors, and (*3*) tumors originating in the postcricoid area. Most cases originate in the hypopharynx, with the lower pole of the tonsil, aryepiglottic fold, and wall of the hypopharynx being the main areas of attachment.

Nearly one-fourth of the patients present with more than one synchronous lipoma. Respiratory symptoms are dependent on the position of the lipomas. Two of the 24 patients reviewed by Mansson et al.[12] suffocated.

The tumors may become large and, because nearly all are pedunculated, may make a startling presentation through the mouth. Microscopic examination shows that the fat is mature and often fibrotic and separated by fibrous trabeculae.

It is claimed that 20% of all benign pedunculated intraluminal tumors in the esophagus are lipomas.[13] Almost all esophageal lipomas originate in the upper part of the esophagus with their stalk at the level of or just below the cricopharyngeal muscle.

Lipomas of the intrinsic larynx are less common and account for approximately 0.1% of all benign laryngeal neoplasms.[14] The ventricles are said to be the sites of predilection.

LIPOSARCOMAS

Liposarcomas are considered among the most unusual forms of malignancy affecting the head and

Table 3. Clinical behavior of the different histologic types of liposarcoma (all anatomic sites).[a]

Histologic type	Recurrence rate	5-year survival
Well-differentiated (adult)	53%	85%*
Myxoid	53%	77%
Pleomorphic	73%	21%
Round-cell	85%	18%

[a]*Based on data from Enzinger and Winslow.*[18]

neck. This certainly cannot be judged on the basis of the literary effort expended in recordings of single cases and in periodic reviews of the literature. In the present review, we have attempted to collect all authentic cases and to correct the incompleteness of preceding tabulations.[15-18] Table 2 presents the anatomic sites of origin of 50 documented liposarcomas of the head and neck as of mid 1979. Analysis of these cases plus 9 cases of liposarcoma occurring in the skull, scalp, and meninges (which are excluded from Table 2) showed that 19 of the 61 patients died of their tumor, a mortality rate of 31%.

Surgical removal has been the mainstay of treatment. The occasional favorable result after irradiation and combination therapy indicates that more experience is needed in such treatment for this malignancy of the supporting tissue.

Many pathologists have placed an undue significance on stains to demonstrate lipid. Not only do some liposarcomas lack demonstrable lipids (this lack is especially noticeable in round-cell and pleomorphic liposarcomas, see below), many other supporting-tissue tumors manifest lipid, especially in areas of degeneration.

Lipoblastic tumors in children (lipomas and liposarcomas) in any anatomic location are unusual when compared to those in adults. The majority of the liposarcomas in this age group are well-differentiated, and metastases are rare.[21]

Liposarcomas have been histologically classified into 4 major subtypes: myxoid, round-cell, pleomorphic, and well-differentiated or adult-type.[19] This is more than an academic exercise since there is good correlation with biologic activity and prognosis. As shown in Table 3,[19,20] survivals of patients with myxoid and well-differentiated liposarcomas (all anatomic sites) are much better than those of patients with round-cell and pleomorphic liposarcomas, but recurrence rates exceed 50% for all histologic types.

Myxoid Liposarcoma. This is the most common of the histologic subtypes and accounts for nearly

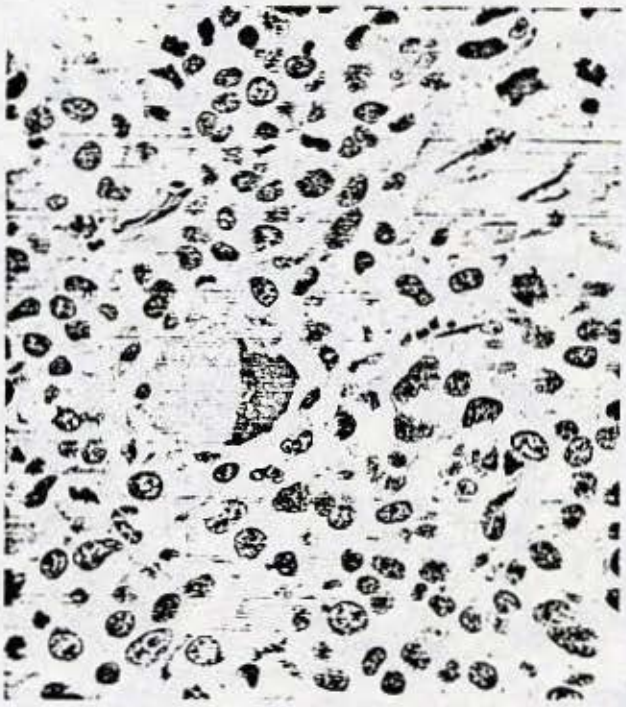

Figure 7. Pleomorphic liposarcoma. Hematoxylin and eosin, ×85

one-half of all liposarcomas[19] and for most liposarcomas of the head and neck.[20] The tumor is composed of 3 main elements: (*1*) proliferating lipoblasts in various stages of differentiation, (*2*) a delicate plexiform capillary vasculature, and (*3*) a myxoid matrix containing abundant hyaluronidase-sensitive acid mucopolysaccharides.

The great majority of proliferating cells in the myxoid liposarcoma resemble the cells in fetal (18 weeks gestation) fat. Only with lipid deposition and enlargement of the cells do they approach the appearance of mature fat cells. There is an almost complete absence of mitotic figures.

The capillary vasculature is one of the most distinctive features of the myxoid liposarcoma. It is most prominent when the cells are most primitive.

Most myxoid liposarcomas maintain a uniform pattern, even after treatment and recurrences. Transition to more biologically malignant forms is seen, however, and should be sought in multiple sections.

Round-Cell Liposarcoma. This type is characterized by an excessive proliferation of uniform and rounded cells. A "hypernephroid" appearance may be conveyed. Lipid formation appears inhibited, and there is little intercellular myxoid matrix.

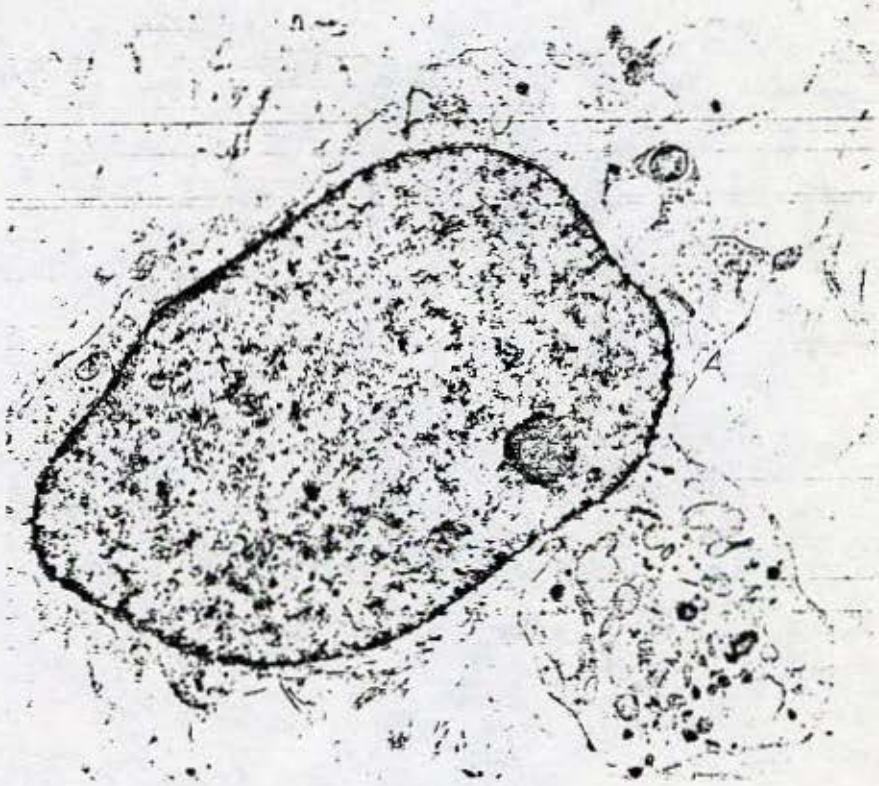

Figure 8. Electron micrograph of a liposarcoma cell. Note the characteristic osmophilic lipid droplet (upper right) and cytoplasmic extensions. Uranyl acetate and lead citrate, ×11,200.

Pleomorphic Liposarcoma. This form is probably the least frequently recognized of all liposarcoma. These tumors are characterized by an extreme degree of cellular pleomorphism and bizarre giant cells. In some forms, large giant cells with numerous lipid droplets of varying size are present (Figs. 7 and 8). Multinucleated cells are common. Many of the giant lipoblasts are among the largest cells produced in human neoplasms. Smaller polygonal and spindle-shaped lipoblasts are intermingled with the giant cells. A prominent acidophilia may be present in the giant cells.

Well-Differentiated (Adult-Type) Liposarcoma. There are 2 forms of this histologic type—well-differentiated "lipoma-like" and well-differentiated sclerosing. Tumors best considered as atypical lipomas (see above) may have been included in the well-differentiated "lipoma-like" group.[1] Sclerosing liposarcomas are not common and have a strong predilection for the retroperitoneum.

REFERENCES

1. Evans HL, Soule EH, Winkelmann RK: Atypical lipoma, atypical intramuscular lipoma, and well differentiated retroperitoneal liposarcoma. A reappraisal of 30 cases formerly classified as well differentiated liposarcoma. *Cancer* 43:574–584, 1979.
2. Dionne GP, Seemayer TA: Infiltrating lipomas and angiolipomas revisited. *Cancer* 33:732–738, 1974.
3. Angervall L, Dahl I, Kindbloom LG, Säve-Soderbergh J: Spindle cell lipoma. *Acta Pathol Microbiol Scand* [A] 84:477–487, 1976.
4. Enzinger FM, Harvey DA: Spindle cell lipoma. *Cancer* 36:1852–1859, 1975.
5. Carlsen A, Thomsen M: Different clinical types of lipomatosis. Case report. *Scand J Plast Reconstr Surg* 12:75–79, 1978.
6. Chung EB, Enzinger FM: Benign lipoblastomatosis. An analysis of 35 cases. *Cancer* 32:482–492, 1973.
7. Lacomme Y: Hibernome cervical. *Rev Laryngol Otol Rhinol* (Bord) 94:66–70, 1973.
8. Lawson W, Biller HF: Cervical hibernoma. *Laryngoscope* 86:1258–1267, 1976.
9. Levine GD: Hibernoma. An electron microscopic study. *Hum Pathol* 3:351–359, 1972.
10. Hatziotis JCh: Lipoma of the oral cavity. *Oral Surg* 34:511–524, 1971.
11. Eagle WW: Lipoma of the epiglottis and lipoma of the hypopharynx in the same patient. *Ann Otol Rhinol Laryngol* 74:851–862, 1965.
12. Mansson I, Wilske J, Kindblom L-G: Lipoma of the hypopharynx. A case report & a review of the literature. *J Laryngol Otol* 92:1037–1043, 1978.

13. Elner A, Palm, NG: Pedunculated intraluminal fibrolipoma of the oesophagus. *Acta Otolaryngol* (Stockh) 82:457–462, 1976.
14. New GB, Erich JB: Benign tumors of the larynx. *Arch Otolaryngol* 28:841–910, 1938.
15. Baden E, Newman R: Liposarcoma of the oropharyngeal region. Review of the literature and report of two cases. *Oral Surg* 44:889–902, 1977.
16. Hudson C, Cove P, Adekeye EO: Liposarcoma of the head and neck: report of case and review of the literature. *J Oral Surg* 36:380–383, 1978.
17. Kindblom L-G, Angervall L, Jarlstedt J: Liposarcoma of the neck. A clinicopathologic study of 4 cases. *Cancer* 42:774–780, 1978.
18. Saunders JR, Jaques DA, Casterline PF, Percarpio B, Goodloe S: Liposarcomas of the head and neck. A review of the literature and addition of four cases. *Cancer* 43:162–168, 1979.
19. Enzinger FM, Winslow D: Liposarcoma: a study of 103 cases. *Virchows Arch* [*Pathol Anat*] 335:367–388, 1962.
20. Perlito A: Primary pleomorphic liposarcoma of the larynx. *J Otolaryngol* 7:161–166, 1978.
21. Kauffman SL, Stout AP: Lipoblastic tumors of children. *Cancer* 12:912–925, 1959.

Case 7. Floor of mouth: adult rhabdomyoma

Extracardiac rhabdomyomas are actually less common than the cardiac type which is often associated with the phakomatoses (tuberous sclerosis, neurofibromatosis). Extracardiac rhabdomyomas are considered as true neoplasms of skeletal muscle, while the cardiac form is thought to be a developmental abnormality and perhaps an example of a glycogen storage disease

Extracardiac rhabdomyomas also occur in two histologic forms: adult and so-called fetal types.

The more common, adult variety, usually occurs in the head and neck region of young adult males. The fetal rhabdomyomas have been subclassified into a myxoid variant and a cellular variant. The former has a predilection for the postauricular region of infants and the vulvovaginal area of middle age women. The cellular variant occurs primarily in the head and neck region of adult males.

In the oral cavity, the majority of tumors have occurred in the floor of the mouth, followed by soft palate, tongue, and buccal mucosa.

A few adult rhabdomyomas may be multifocal. Local recurrence is unusual. In no instance has a rhabdomyoma demonstrated aggressive local growth or metastases.

Both forms are well-circumscribed and generally exhibit a prominent vascularity. The adult form is composed of large ovoid or polygonal cells with granular eosinophilic cytoplasm. Vacuoles

are prominent and are mainly located at the periphery of the cytoplasm. Extreme degrees of vacuolization impart a "spindle web" appearance. Cross-striations are usually demonstrable. The fetal type mainifest strap-shaped cells in a haphazard arrangement and cross-striations are difficult to find.

Ultrastructure examination of adult rhabdomyomas demonstrates myofibrils irregularly arranged with rod-like Z-band material. Tumor cells are often packed with mitochondria bearing lamella inclusions. Fetal types manifest muscle cells in different stages of differentiation and only a few cells contain rod-like Z-band material. Mitochondria are few.

Konrad, E.A., Meister, P. and Hubner, G.: Extracardiac rhabdomyoma. Cancer 49:898-907, 1982.

Neville, B.W., and McConnel, F.M.S.: Multifocal adult rhabdomyoma. Arch. Otolargngol. 107:175-178, 1981.

Corio, R. L, and Lewis, D.M.: Intraoral rhabdomyomas. Oral Surg. 48:525-531, 1979.

Di Sant'Agnese, P.A., and Knowles, D.M.: Extracardiac rhabdomyomas: a clinicopathologic study and review of the literature. Cancer 46:780-789, 1980.

22. Dehner LP, Enzinger FM, Font RL: Fetal rhabdomyoma. Analyses of nine cases. *Cancer* 30:160–166, 1972.
23. Guerbaoui PWM: Rhabdomyome foetal. Etude histologique et ultrastructurale d'une nouvelle observation. *Virchows Arch [Pathol Anat]* 371:59–67, 1976.
24. Weitzner S, Lockey MW, Lockard VG: Adult rhabdomyoma of soft palate. *Oral Surg* 47:70–73, 1979.
25. Silverman JF, Kay S, Chang CH: Ultrastructural comparison between skeletal muscle and cardiac rhabdomyomas. *Cancer* 42:189–193, 1978.
26. Tanner NSB, Carter RL, Clifford P: Pharyngeal rhabdomyoma: an unusual presentation. *J Laryngol Otol* 92:1029–1036, 1978.
27. Fu Y-S, Perzin KH: Nonepithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx: a clinicopathologic study. V. Skeletal muscle tumors (rhabdomyoma and rhabdomyosarcoma). *Cancer* 37:364–376, 1976.
28. Ferlito A, Frugoni P: Rhabdomyoma purum of the larynx. *J Laryngol* 99:1131–1141, 1975.

Case 8. Neck, extra-abdominal desmoid

Desmoid tumors offer challenges in diagnosis and also management. They represent one point in a spectrum of fibrous tumors and tumor-like conditions that range from keloids to fasciitis, Dupuytren's contracture to desmoid and fibrosarcomas.

The best known are those of the abdominal wall where many appear to be pregnancy-related. Despite their relatively innocuous histologic appearance, the desmoid at either abdominal or extra-abdominal sites, has a high incidence of local recurrence; as high as 70% in some series. The seminar case is characteristic of the difficulties in completely removing this lesion whose behavior qualifies it for its characterization of fibrosarcoma, grade I.

The desmoid type of fibromatosis has a fairly uniform histologic appearance. Typically the lesional tissue is of a moderately cellular interlacing bundles of elongated fibroblasts with no pleomorphism and little or absent mitotic activity. Variable amounts of fibrillar collagen is seen. A feature which I have found distinctive is the presence of slit-like vascular spaces, not related to inflammation and like that seen in other tumors of myofibroblastic origin such as the angiofibroma. The lesion is always infiltrative.

The tumors are deep seated and arise from fascia or the aponeurosis. The principal location for extra-abdominal desmoids is the shoulder, followed by the chest wall and back and the mesentery. The head and neck, in the AFIP series, had an incidence of 9.5%

Metastases do not occur but its behavior is predicted on the recurrences and often non-resectability.

Systemic chemotherapy appears to be a useful adjunct in the treatment of desmoid fibromatosis.

Khorsand, J. and Karakousis, C.P.: Desmoid tumors and their management. Am J. Surg. 149:215-218, 1985.

Melrose, R.J., and Abrams, A.M.: Juvenile fibromatosis affecting the jaws. Oral Surg. 49:317-324, 1980.

Goepfert, H., Cangir, A., Ayala, A., Eftekhari, F.: Chemotherapy of locally aggressive head and neck tumors in the pediatric age group. Desmoid fibromatosis and nasopharyngeal angiofibroma. Am. J. Surg. 144·437-445, 1982.

Allen, P.W.: The fibromatoses: A clinicopathologic classification based on 140 cases. Am. J. Surg. Pathol. (Part I). 1:225-270, 1977.

Masson, J.K., and Soule, E.H.: Desmoid tumors of the head and neck. Am. J. Surg. 112:615-622, 1966.

Enzinger, F.M., and Weiss, S.W.: Soft Tissue Tumors, C.V. Mosby, St. Louis, 1983.

Case 9. Leiomyosarcoma, maxillary sinus

The history of a cutaneous facial melanoma ~~in the patient~~ makes the exclusion of metastatic melanoma a requirement in this patient; this despite the fact that melanomas metastatic to the paranasal sinuses are unusual.

The present case's tumor was studied immunochemically with the following results; (1) S-100 protein antigen negative, (2) desmin negative, (3) smooth muscle myosin, positive.

Leiomyosarcoma of the sinonasal tract is a rare neoplasm; 17 cases reported between 1958 and 1985. At least half of the diagnoses were made on the basis of light-optic examination only without exclusion of sarcomatoid carcinoma, desmoplastic melanoma, synovial sarcoma, fibrosarcoma or neurofibrosarcoma, the principal differential diagnoses.

The nasal fossa and the maxillary antrum have accounted for the preponderance of the sites of origin.

The outlook for patients is dismal. Half of the patients are dead within three-years and a 20% five-year survival is optimistic. Invasion of the orbit is disastrous. There are no survivors with orbital invasion, regardless of the treatment protocol.

The oral cavity shares with the sinonasal tract the distinction of having few malignant smooth-muscle neoplasms. In the 25 years prior to 1981, only eight cases had been published, but 20% of

all smooth-muscle tumors of the oral cavity are malignant and manifest the same degree of adverse biologic behavior as those in the sinonasal tract.

The accompanying tables present a recent tabulation of sinonasal leiomyosarcomas and follow-up status.

Fu, Y-S, and Perzin, K.H.: Non-epithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx: A clinicopathologic study. IV. Smooth-muscle tumors (leiomyoma, leiomyosarcoma). Cancer 35:1300-1308, 1975.

Josephson, R.L., Blair, R.L., and Bedard, Y.C.: Leiomyosarcoma of the nose and paranasal sinuses. Otolaryngol. Head and Neck Surg. 93:270-274, 1985.

Kratochvil, F.J., MacGregor, S.D., Hewan-Lowe, K., and Allsup, H.W.: Leiomyosarcoma of the maxilla. Report of a case and review of the literature. Oral Surg. 54:647-655, 1982.

Bures, J.C., Barnes, L., Mercer, D.: A comparative study of smooth-muscle tumors utilizing light and electron microscopy, immunocytochemical staining and enzymatic assay. Cancer 48:2420-2426, 1981.

Farman, A.G., and Kay, S.: Oral leiomyosarcoma. Report of a case and review of the literature pertaining to smooth-muscle tumors of the oral cavity. Oral Surg. 43:402-409, 1977.

Sinonasal Leiomyosarcomas

Apparent Site of Origin	Number of Cases
Nasal fossa	7
Antrum	5
Ethmoidal	1
Frontal/Sphenoid	0
Combination - primary indeterminant	5
	18

Leiomyosarcomas of Sinonasal Tract: Follow-up

11 - Dead (6 mos - 3 yrs)

5 - Alive (1 yr - 2 yrs)

2 - Unknown

Case 10. Paranasal sinus and nasal cavity: malignant rhabdoid tumor

Nearly exclusively a lesion of infancy and young childhood, the malignant rhabdoid tumor is also only rarely reported as an extrarenal neoplasm.

The light-microscopic features of malignant rhabdoid tumor are distinctive but one of its more characteristic features, intracytoplasmic eosinophilic inclusions, is non-specific. The latter is due to large filamentous aggregates (approximately 6-10 nm in diameter). Immunocytochemical reactions for myoglobin are claimed to be uniformly negative and those for muramidase have been variable. Positive staining for vimentin in the filament clusters support the contention of a mesenchymal origin for the neoplasm.

Malignant rhabdoid tumors lack the strap cells and prominent cytoplasmic spindling of embryonal rhabdomyosarcoma. Ultrastructural absence of skeletal muscle differentiation also aid in this distinction. More difficult to distinguish, however, is a high-grade epitheloid sarcoma. Cytologically and ultrastructurally, the polygonal cells with eosinophilic filamentous inclusions seen in both tumor types are not distinguishable. Immunohistochemically, both are also composed of the mesenchymal intermediate filament, vimentin. The distinction between the two is largely based on their growth patterns, the nature of the non-filamentous cells, and the tumor's location. A nodular or pseudonodular growth pattern characterizes epitheloid sarcoma. A pseudogranulomatous appearance may be conveyed by palisading about zones of necrosis and the non-filamentous cells typically have abundant eosinophilic cytoplasm. Epitheloid sarcoma is also typically

a subcutaneous or superficial soft tissue neoplasm. The malignant rhabdoid tumor is diffuse in growth and manifests no nodularity or pseudogranulomatous appearance. It is also a visceral and not a superficial neoplasm. By 1984, nine extrarenal examples had been reported (head and neck, chest wall, retroperitoneum, pelvis, arm, thymus and subcutaneum).

Malignant rhabdoid tumor is a highly aggressive and unusually fatal neoplasm. In most instances, multi-nodal therapy has failed to control the neoplasms.

While the vimentin filaments point to a mesenchymal origin of the tumor, this does little justice to its complicated history. The tumors have been related to a hypercalcemic syndrome without macroscopic bone metastases, a puzzling ectopic hormone secretion (PTH), and an association with primitive neuroectodermal tumors of the brain.

Frierson, H.F., Mills, S.E., and Innes, D.J., Jr.: Malignant rhabdoid tumor of the pelvis. Cancer, 55:1963-1967, 1985.

Rutledge, J., Beckwith, J.B., Benjamin, D. and Haas, J.E.: Absence of immunoperoxidase staining for myoglobin in malignant rhabdoid tumor of the kidney. Pediatr. Pathol. 1:93-98, 1983.

Bonnin, J.M., Rubenstein, L.J., Palmer, N.F., and Beckwith, J.B.: The association of embryonal tumors originating in the kidney and in the brain. A report of seven cases. Cancer, 54, 2137-2146, 1984.

Rousseau-Merck, M-F, Nogues, C., Nezelof, C., Marin-Cudraz, B. and Paulin, D.: Infantile renal tumors associated with hypercalcemia. Characterization of immediate-filament clusters. Arch. Pathol. Lab. Med. 107:311-314, 1983.

Mayes, L.C., Kasselberg, A.G., Roloff, J.S. and Lukens, J.N.: Hypercalcemia associated with immunoreactive parathyroid hormone in a malignant rhabdoid tumor of the kidney (Rhabdoid Wilm's tumor). Cancer, 54, 882-884, 1984.

Case 11. Buccal gingiva, hemangiopericytoma

Hemangiopericytomas continue to be either over- or under-diagnosed. The seminar case is a rather classic example which should not be confused with a synovial sarcoma, hemangioma or angiosarcoma, or a mesenchymal chondrosarcoma. Predicting its biologic behavior on purely histologic grounds, however, is another matter. It is likely that site, depth and size are the important determinants. The cellularity of your case, despite absence of significant numbers of mitosis and necrosis would lead one to regard the lesion as biologically aggressive, at least with respect to recurrences.

Sinonasal hemangiopericytomas do not share the morbidity of soft tissue hemangiopericytoma, a tumor with a predilection for the soft tissues of the head and neck in infants and neonates is a benign tumor, despite histologic evidence to the contrary.

Head and neck hemangiopericytomas are considered along with several other vasoformative lesions in the head and neck in the accompanying reprint.

THE PATHOLOGY OF HEAD AND NECK TUMORS: VASOFORMATIVE TUMORS, PART 9B

JOHN G. BATSAKIS, MD, and DALE H. RICE, MD

Abstract: There are three principal malignant vasoformative tumors that can be found in the head and neck—hemangiopericytoma, angiosarcoma, and Kaposi's sarcoma. All are uncommon and provide challenges for the pathologist and the therapist both. The histogenesis of each tumor is different. Kaposi's sarcoma has many features which suggest that it is an altered immune-response disease. Angiosarcoma is a malignancy of endothelium. Hemangiopericytoma is a tumor whose cell of origin is considered to be the perithelial pericyte. The general prognosis for patients with Kaposi's sarcoma is good. The biologic course of a hemangiopericytoma is variable and unpredictable, but there appears to be a site dependency. Angiosarcomas, particularly high grade lesions, are resistant to therapy.

HEAD & NECK SURGERY 3:326-339 1981

Compared with benign forms, malignant vasoformative tumors are uncommon lesions in the head and neck. They may be grouped into two categories: those arising from endothelial cells (angiosarcoma and Kaposi's sarcoma), and those tumors arising from the perithelial pericyte (hemangiopericytoma).

The relative rarity of the tumors, and the broad spectrum of histologic appearances manifested by each, always provide a diagnostic challenge for the surgical pathologist. In this report, we review the clinicopathologic features of the malignant vasoformative tumors as they present in the head and neck.

BENIGN VASOFORMATIVE TUMORS

Reactive or Reparative Vascular Lesions. Several vascular and/or endothelial proliferations in response to injury or presumed endothelial stimulation may simulate, and indeed be difficult to separate from, hamartomas or neoplasms of the endothelium.

Pyogenic granulomas. These lesions are reactions to injury and are characterized by exuberant granulation tissue that may be indistinguishable microscopically from hemangioma. Endothelial proliferation and the formation of numerous vascular spaces dominate, but fibroblastic and inflammatory components contribute. Surface ulceration is often present, or evidence of its past presence is seen (Fig. 1).

The often alarming growth of a pyogenic granuloma is due to an increased rate of cell division of both epidermal/mucosal and endothelial compartments, and also to an accumulation of edema and inflammatory cells.

Some histologic features helpful in the differential diagnosis between hemangioma and pyogenic granuloma include the following.

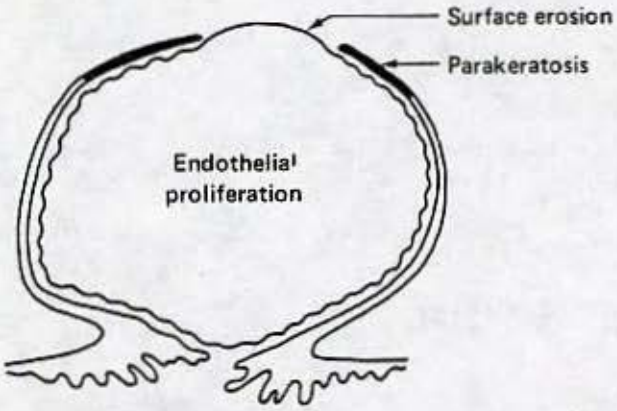

Figure 1. Schematic diagram of a pyogenic granuloma. Note the epithelial collar at the base.

1. The pyogenic granuloma is circumscribed.
2. The pyogenic granuloma shows variation in the degree of proliferation and vessel size from the base to the surface (Fig. 2), whereas the hemangioma may not.
3. The pyogenic granuloma's epithelium tends to surround the deeper portions of the tumor, whereas this is not usually seen in a hemangioma.

Since pyogenic granulomas are reactions to injury, they may occur at any mucosal site where trauma is likely. In the oral cavity they are found in the following locations in descending order of frequency: gingiva, lips, tongue, buccal mucosa, palate, mucolabial or mucobuccal folds, and alveolar mucosa of edentulous areas. Gingival sites account for 65%–70% of the examples.[1] The upper gingiva is involved more frequently than the lower, and most often in the upper facial region. The time between diagnosis and operation varies (mean 8.6 months).

In the nasal cavity, the anterior septal area and inferior turbinates are sites of predilection.

"Hemangiomas of pregnancy." Vascular hemangiomatous lesions associated with pregnancy—"hemangiomas of pregnancy"—are histologically indistinguishable from pyogenic granulomas except for showing less evidence of overlying ulcers. These vascular lesions can involve any visceral, mucosal, or epidermal site. Hemangiomas of pregnancy occurring in the mouth have been reported more frequently than those occurring in the nose. The gingiva is the preferred site in the mouth, and Little's area or Kiesselbach's triangle is the preferred site in the nasal cavity.[2,3]

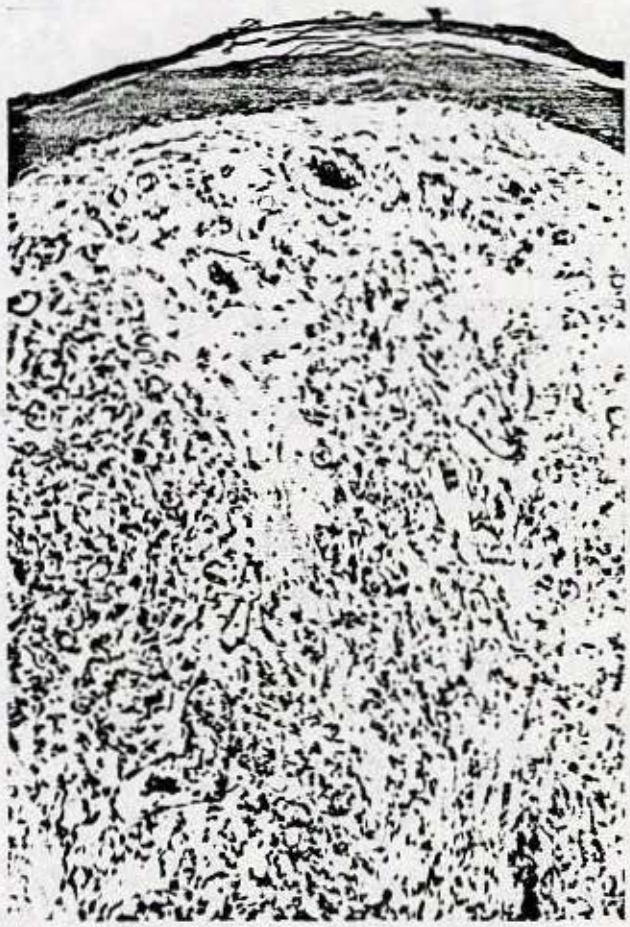

Figure 2. Pyogenic granuloma of nasal septum. Note the keratotic mucosa and the mixture of variably sized vascular spaces. Hematoxylin and eosin, ×60.

The pregnancy tumors usually appear at about the third month of pregnancy and gradually increase in size until gestation is over. Following parturition, they subside and may completely vanish. Complete regression is unusual, and the lesions persist in an involuted state until the next pregnancy.

The fully developed tumor is pedunculated or polypoid but also may be sessile. Unless it is traumatized, gross or microscopic evidence of ulceration is not present.

Other benign vascular lesions. Pseudopyogenic granulomas, which are unrelated to pyogenic granulomas, are benign and vasoproliferative, occurring mainly in or around the ears, and occasionally on the face, neck, or scalp. A prominent inflammatory infiltrate with numerous eosinophils and mast cells distinguishes this lesion from pyogenic granuloma.

Two benign and usually intravascular lesions with a predilection for the subcutaneous tissues of the head and neck are: (*1*) intravascular papillary

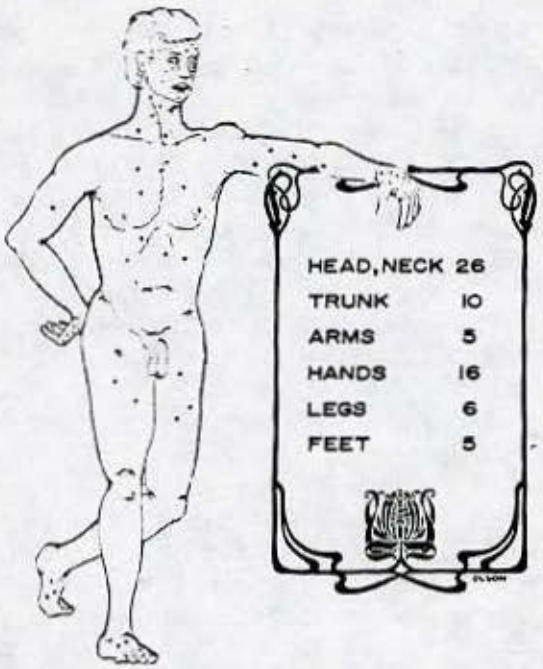

Figure 3. Anatomic distribution of 68 lesions of intravascular papillary endothelial hyperplasia (intravascular angiomatosis). Note the predilection for the head and neck.

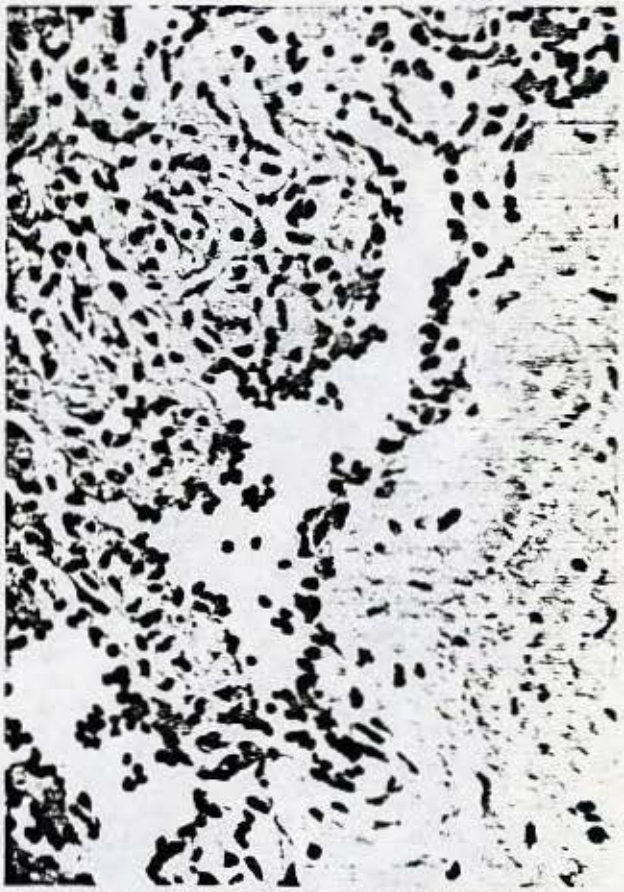

Figure 4. Intravascular papillary endothelial hyperplasia (intravascular angiomatosis). Compare the bland endothelial nuclei of this lesion with those of the angiosarcoma in Figure 8. Hematoxylin and eosin, ×160.

endothelial hyperplasia (intravascular angiomatosis) (Fig. 3), and (2) intravenous pyogenic granuloma.[4,5]

Intravascular papillary endothelial hyperplasia is an often exuberant proliferative lesion that may be misdiagnosed as an angiosarcoma.[6] The lesion is most common in large intravenous thrombi and emboli where it represents a peculiar papillary form of organization. Nearly all the lesions are found in the subcutis but may occur within any vascular space, even in benign vascular tumors such as hemangiomas. An intravascular location, absence or rareness of mitoses, and rareness of solid cellular areas are characteristics of this lesion that exclude a diagnosis of angiosarcoma (Fig. 4). The ultrastructural features of the vessels in granulation tissue and those in papillary endothelial hyperplasia are similar.

Intravenous pyogenic granulomas develop in or adjacent to the wall of a vein. Their microscopic appearance should not be confused with that of vascular malignancy or intravascular papillary endothelial hyperplasia. The organization and histologic characteristics of the intravenous pyogenic granuloma are similar to those of other pyogenic granulomas that are not complicated by inflammatory alterations. The lesion usually presents as an intraluminal polyp attached to a wall of a vein by a fibrovascular stalk.[5]

Arteriovenous Fistulae. Arteriovenous fistulae do not regress and may produce a regional gigantism. The cirsoid form of the arteriovenous fistula is actually a racemose aneurysm composed of turgid venous tributaries. These tend to develop during childhood, are quite painful, and do not involute.

Glomus tumors. The glomus tumor (glomangioma), very likely a hamartoma derived from specialized arteriovenous anastomoses called glomus bodies, is primarily a lesion of the reticular dermis. The glomus body is an S-shaped 60- to 200-μm structure consisting of the vascular anastomosis and related vessels and nerves; the whole body is enclosed in a connective tissue capsule.[7]

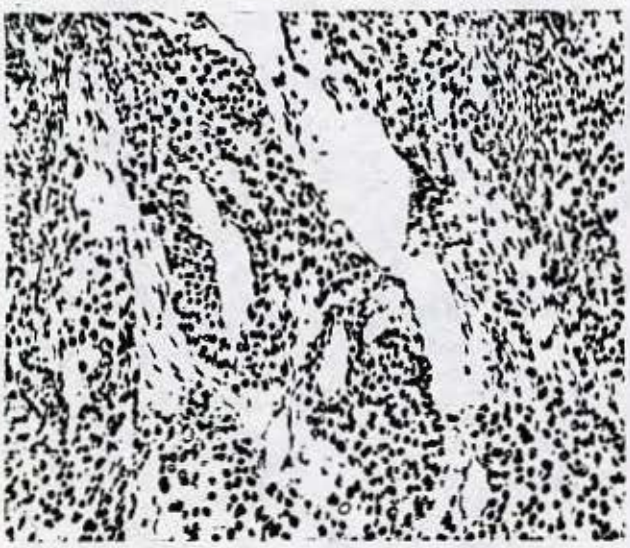

Figure 5. Glomus tumor unrelated either to hemangiopericytoma or paraganglioma except for the common aggregation of the smooth-muscle cells around vascular spaces. Hematoxylin and eosin, ×50.

Although the tumor was originally considered to be of pericytic origin, it is now fairly well established that it originates primarily from smooth muscle.[8]

Most glomus tumors occur in the extremities where they are often subungual. They are seen most often in adults, but are not unknown in children.[7] In nearly every instance, pain is the predominant clinical complaint.[7]

The head and neck region is a rare site for glomus tumors. The neck, nasal cavity, and paranasal sinuses have been reported as sites in individual case reports.

Glomus tumors tend to reproduce the basic structure of the glomus body with either a cellular or a vascular component dominating (Fig. 5). When the vascular element proliferates, there is the formation of large, irregular channels outlined by a thin mantle of glomus cells. If the glomus cells proliferate to form solid masses, the vascular lumina are compressed to slits, and a cellular tumor results.[9] The vascular form of the glomus tumor is often multiple; the cellular form is solitary and retains the encapsulation of the glomus body.[10] It is of interest that the cellular forms are most often symptomatic.

Conservative surgical removal is effective. Some glomus tumors manifest a locally infiltrative character that may lead to recurrence. No

MALIGNANT VASOFORMATIVE TUMORS

Angiosarcomas. Angiosarcomas are not common, but they have a tendency to afflict the head and neck, particularly the scalp and facial soft tissues. Girard et al.[11] found that 14 of 28 cutaneous angiosarcomas presented in this anatomic region. Nevertheless, even major cancer centers do not have many cases for review. Bardwil et al.,[12] from the M. D. Anderson Hospital, reviewed 7 cases between 1963 and 1967; Farr et al.[13] reviewed 10 cases seen at Memorial Sloan-Kettering Cancer Center in New York City between 1930 and 1969; and Hodgkinson et al.[14] reviewed 13 patients seen over a 50-year period at the Mayo Clinic.

Cutaneous angiosarcoma of the face and scalp has been well defined clinically and pathologically. The scalp is the dominant area of primary involvement. The clinical appearance of the cutaneous angiosarcoma is often such that a presumptive diagnosis can be made on that basis alone. Because of intrinsic difficulties in the surgical pathologic diagnosis, the pathologist should always be completely informed of the clinical presentation.

Angiosarcoma of the skin has a marked predilection for the elderly, and males predominate over females by a 4:1 ratio. Multiple lesions are found in nearly two-thirds of the patients either at the time of initial diagnosis or later. Lymphadenopathy may also be present at the time of initial examination.

Grossly, there are 3 primary presentations: an ulcerating type; a diffuse, superficial, spreading type; and a nodular form. Ulceration, if extensive, may obscure these features.

The tumors are usually blue or purple and often manifest a peripheral zone of erythema and satellitosis. Intralesional hemorrhage and spontaneous bleeding are common. In the flat forms, the gross resemblance to a contusion may be deceptive, and in the nodular form, a melanoma may be suggested.

At surgery, the lesions present no encapsulation and have a decided tendency to spread through adjacent soft tissues for surprising distances, especially in the scalp. In addition, the neoplasms extend deeply, reaching fascial planes, bone, or cartilage. A characteristic feature of angiosarcomas is that even though they involve the dermis extensively, they tend to grow around skin adenexae and leave them intact. The deceptive gross extent of the lesions is such that the surgeon must often deviate from the preoperative plan of excision in order to encompass the tumor during

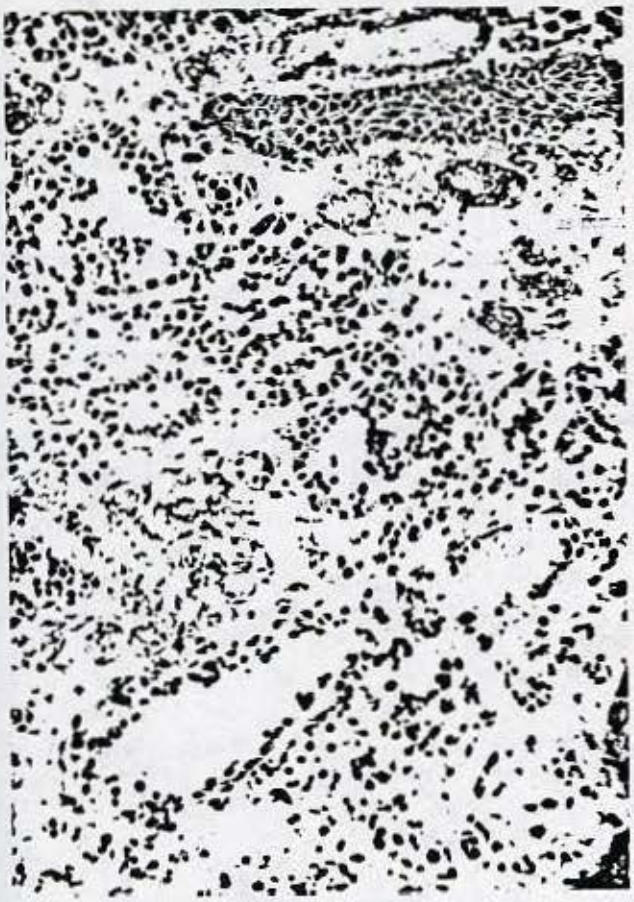

Figure 6. Angiosarcoma (low-grade) of nasal cavity. Except for the dark neoplastic cells lining the vascular spaces, the tumor could be misjudged as a pyogenic granuloma. Hematoxylin and eosin, ×50.

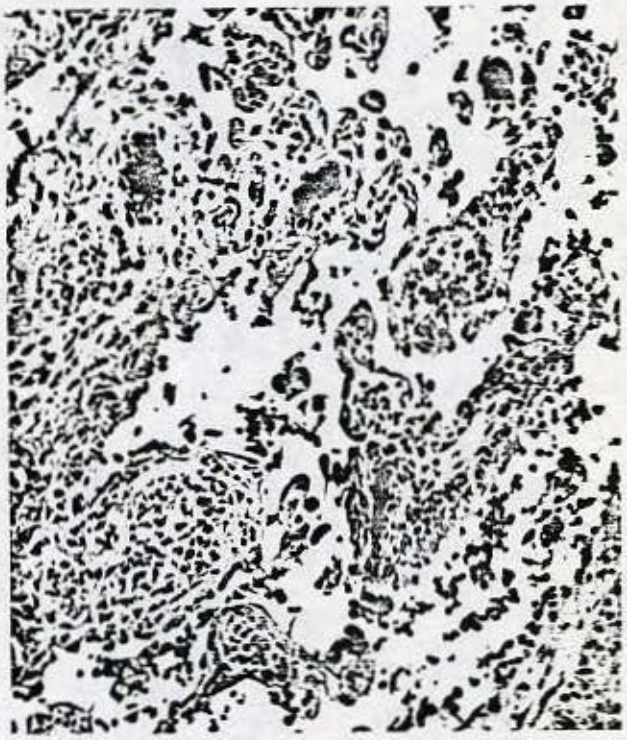

Figure 7. Angiosarcoma of scalp. Papillary cores of connective tissue contain malignant endothelial cells. Hematoxylin and eosin, ×40.

The surgical pathologic diagnosis of angiosarcoma first requires a prepared mind. Lack of this prerequisite and the failure to find histologic features indicative of the diagnosis usually lead to diagnoses of melanoma, undifferentiated carcinoma, and even spindle-cell sarcoma.

At least 2 histologic grades of angiosarcoma exist: low-grade and high-grade (undifferentiated). Angiosarcomas of the scalp are more likely to be high-grade tumors. On superficial examination, low-grade angiosarcomas may resemble capillary hemangiomas or even pyogenic granulomas (Fig. 6). However, the vascular spaces are lined by large, plump endothelial cells, the vascular spaces penetrate stroma, and there are usually papillary fronds of endothelial cells projecting from the walls of the spaces into lumina (Figs. 7 and 8). High-grade (undifferentiated) angiosarcomas are diffusely cellular and infiltrative (Fig. 9). Anastomosing dermal channels are lined by atypical cells that are often

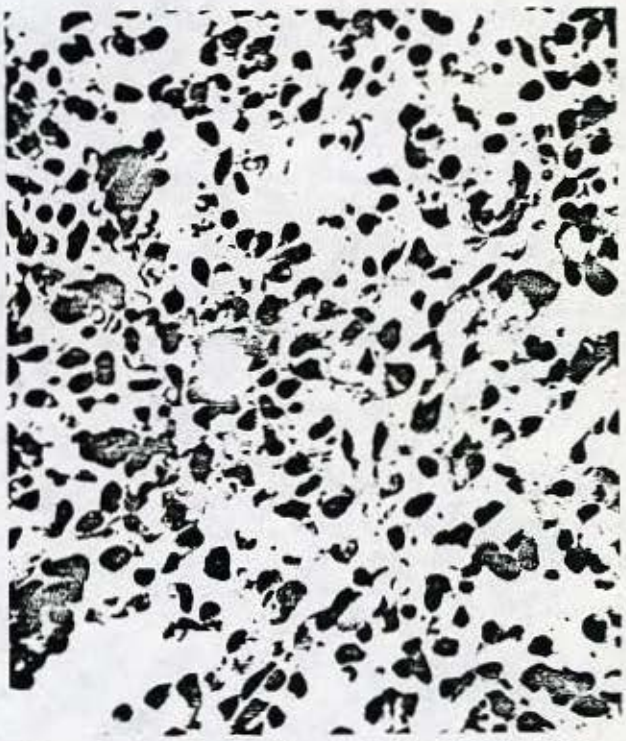

Figure 8. Angiosarcoma of scalp. Note the deeply staining nuclei of the endothelial cells and the atypical forms of the latter. Hematoxylin and eosin, ×160.

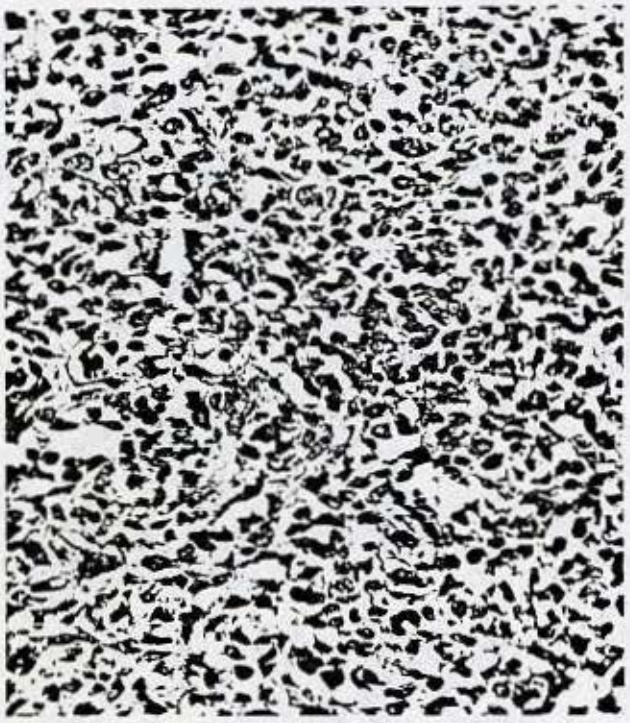

Figure 9. Undifferentiated or high-grade angiosarcoma. The tumor is composed of proliferating endothelium with minimal or no lumen formation. Hematoxylin and eosin, ×60.

spindle-shaped, and these areas are mixed with undifferentiated areas. There is often a sponge-like network in the spindle cell and undifferentiated parts of the tumors. Abnormal mitoses may be plentiful. Associated with both low- and high-grade angiosarcomas are proliferative changes in the vessels at a distance from the main lobules of the neoplasms.

In some difficult cases, fine structural details characteristic of endothelium may have to be identified. In well-differentiated tumors, the appearance of the neoplastic cells may be almost identical to that of normal endothelium:[15] there may be numerous pinocytotic vesicles, well-developed intercellular junctions, cytoplasmic projections into lumina, and an occasional closed-type fenestrum. In undifferentiated tumors, the cells contain pinocytotic vesicles and fibrils in their cytoplasm. The formation of primitive lumina as an index of angiogenesis is an important ultrastructural finding.

A recent survey reported 89 cases of angiosarcoma involving the skin and soft tissues of the head and neck.[16] Data from several series[11-14] indicate that the scalp is the most commonly involved site of the skin and soft tissues of the head and neck (30 cases total in the scalp and 19 total in the skin of the face and neck).

Primary angiosarcomas arising in the structures of the upper airway are unusual. Bankaci et al.[16] could find only 14 published cases of tumors whose origin was in the nasal cavity, paranasal sinuses, or nasopharynx. As of 1979, the maxillary antrum had been cited as a primary focus in 5 cases.[17] It appears that angiosarcomas arising in these locations have a better prognosis than those of the scalp and soft tissues. This observation, if accurate, may be related to the earlier diagnosis, the younger age of the patients, and possibly the higher level of differentiation of the neoplasms that are associated with angiosarcomas in the upper airway.

Observations on survival of patients with cutaneous and soft-tissue angiosarcomas are hampered by small numbers of cases, short follow-up periods, and inclusion of angiosarcomas of visceral sites and hemangiopericytomas in the data for cutaneous and soft-tissue angiosarcomas. Regional metastases to the lymph nodes and lungs are manifested in approximately one-third of the patients. Metastases usually follow a pattern of extensive local growth and recurrences after a failure of local control. The metastases tend to be less differentiated than the primary tumor.

According to Bankaci et al.,[16] Bardwil et al.,[12] and Farr et al.,[13] one-half of the patients with angiosarcoma of the scalp and facial tissues die of their disease within 5 years of diagnosis. Nearly one-quarter of the patients live with persistent or recurrent tumor, and a similar number are apparently "cured." Cures are most likely to be achieved in patients who have not suffered recurrences. Because tumors situated in the nose, ear, or lip usually have an earlier clinical presentation, they have a potentially better chance of cure.

Until recently, surgical excision has been the mainstay of therapy. In many patients, however, recurrences ensue after a short period, and this is followed by a lack of local control. Failure of surgical excision can be attributed, in part, to the diffuse growth exhibited by angiosarcomas, and, in part, to satellitosis and multicentric growth. Rosai et al.[18] advise surgical excision only for lesions that are solitary and well circumscribed. Others are to be treated by irradiation.

Primary malignant bone tumors of an unequivocal vascular origin are rare but may involve the jaw bones where they pose diagnostic and therapeutic problems. Among 1,481 primary malignant bone tumors, Dahlin[19] found 7 angiosarcomas (0.5%). In a series of 626 malignant primary bone tumors reviewed by the Netherlands Committee on Bone Tumors,[20] there were

also 7 cases (1%). In the Swedish Cancer Registry, 6 of 696 primary malignant bone tumors were angiosarcomas.[20] In about one-fourth of the cases, multicentric involvement is present.

Opinions about the malignant potential and clinical course of angiosarcoma of bone vary, but the tumors are generally considered to be less benign than originally thought. Bundens and Brighton[21] conclude that the prognosis is poor; only 8 of 22 patients in their review lived for more than 3 years. In a series of 22 cases presented by Unni et al.,[22] 11 patients died of their disease. Similar statistics for survival are presented by Garcia-Moral,[23] who reports a 5-year survival of 26% for cases reviewed in the literature.

In the head and neck, the skull and mandible have been cited as primary locations for angiosarcoma of bone. Seven of the completely documented cases reviewed by Garcia-Moral[23] were found in these areas: 3 in the skull and 4 in the mandible. All were claimed to be multicentric.

Kaposi's Sarcoma. Despite considerable controversy over the histogenesis of Kaposi's sarcoma, it is now conceded that the neoplasm arises from vasoformative cells. Theories on the pathogenesis of the disease are currently centering around the hypothesis of Warner and O'Loughlin[24] that relates tumor rejection to the development of Kaposi's sarcoma. This suggests that a chronic immunologic interaction between normal and antigenically altered or transformed lymphocytes (such as occurs in a host-vs.-graft reaction) results in production of an angiogenesis factor, in turn evoking an intense proliferation of mesenchymal and endothelial cells, which ultimately develops into Kaposi's sarcoma. In such a chronic and probably low-grade immune response, enhancing factors, recruitment, and oncogenic viruses become additive factors. The finding of herpesviruses or cytomegaloviruses in some cases of Kaposi's sarcoma points to such a sequence. Lymphoma-like changes as well as definable lymphomas in patients with Kaposi's sarcoma also support the host-vs.-graft response theory.

Few neoplastic diseases present with such an unusual mixture of features as Kaposi's sarcoma. The disease has an odd ethnic and geographic distribution. In Europe the disease favors Ashkenazi Jews and Italians from the Po Valley. In the United States, the disease has been observed to occur more often in immigrants from eastern Europe and Italy. A high proportion of patients are noted to be Jewish. American Blacks are also affected by the disease. Kaposi's sarcoma is less rare in Africa, especially in Uganda and parts of southern and central Africa. Despite this apparent concentration in certain racial groups, there is no regular form of inheritance, and familial occurrence is unusual.

Males are involved far more often than females, and most patients are older than 25 years of age when their disease is manifested. A lymphadenopathic form of the disease occurs in children and is associated with lymphomas.

Kaposi's sarcoma usually has its primary clinical manifestations in the skin with the distribution favoring the superior and inferior aspects of the extremities. Involvement of the skin of the head and neck is much less frequent.

Kaposi's sarcoma of the mucous membranes is well known. The upper aerodigestive tracts are involved in approximately 10% of cases. In these cases, the disease is usually advanced and generalized.

In a tabulation of head and neck involvement by Kaposi's sarcoma, Abramson and Simons[25] considered the head and neck dermis, including the skin of the nose, to be the most frequent non-mucous membrane site of the lesions. The oropharynx and larynx are areas of predilection for lesions of the mucous membrane. In the oral cavity, the palate appears to be favored. The lesions at these sites may be solitary or multiple. It is very rare for Kaposi's sarcoma to present in the mucosa before presenting in the skin.

The light microscopic appearance of Kaposi's sarcoma comprises several stages of evolution: (*1*) inflammation, (*2*) proliferation of capillaries, (*3*) angioma, and (*4*) sarcoma.

The predominantly inflammatory stage is not often biopsied and presents a mainly mononuclear infiltrate (lymphocytoid cells, lymphocytes, histiocytes, and plasma cells). The nonspecificity of dilated vascular channels and perivascular infiltrates renders diagnosis at this stage nearly impossible.

On the basis of examination of well-developed lesions, a histologic subclassification of Kaposi's sarcoma into 3 groups has evolved[26]: (*1*) a mixed-cell pattern, (*2*) a spindle-cell or monocellular pattern, and (*3*) an anaplastic pattern. The mixed-cell pattern is characterized by small capillary slits with intervening spindle cells interspersed with well-formed vascular (capillaries and arterioles) spaces (Fig. 10). Extravasated erythrocytes are easily found. The spindle-cell pattern is dominated by proliferating spindle cells and a marked reduction in tumor vascularity. Mitotic activity is

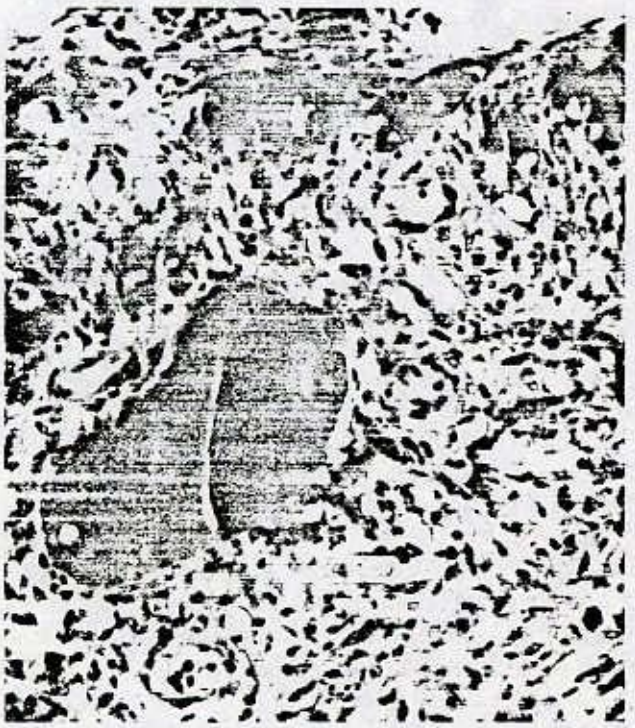

Figure 10. Kaposi's sarcoma in skin. Capillary-sized vessels intermingle with spindle-fibroblast-like cells. Hematoxylin and eosin, ×100.

pronounced, but there are seldom more than 1 mitotic figure per high-power field. Anaplastic tumors exhibit the greatest cellularity and may show nuclear pleomorphism and a marked vascularity.

Prognosis on the basis of histologic appearance alone is difficult to gauge, but the histopathology is useful in predicting the response to therapy in patients with locally aggressive lesions. Mixed-cell tumors usually respond to therapy, whereas anaplastic tumors seldom do. The vascular components of Kaposi's nodules seem to be more sensitive to drug therapy than are the spindle cells.

The growth pattern in skin and mucous membranes may be nodular or plaque-like, but is usually a mixture. Nodules are well circumscribed and distributed nearly equally between the deep dermis, at the level of the sweat glands, and the skin surface, immediately below the epidermis or ulcerating through it. Plaques are more diffuse and more likely to be superficially situated.

Involution coexists with evolution of the nodules or plaques. Degenerative changes in tumor cells, increased collagenization, and endarteritis are microscopic indications of involution.

The general prognosis for patients with Kaposi's sarcoma is good. While the incidence of spontaneous remission cannot be evaluated, a large number of patients report remission of some or all of their nodules at some time during the course of their disease. Classification of the disease according to 3 clinical patterns assists in prognostication: (*1*) nodular, (*2*) locally aggressive, and (*3*) generalized.[27] Patients with nodular disease typically manifest subcutaneous nodules up to 2.0 cm in diameter attached to or involving overlying skin, but not infiltrating into deeper structures. Subcutaneous plaques up to 3.0 cm may be seen in some of the cases in this group. Locally aggressive disease is fungating, vegetative, or florid. Growth is rapid, ulceration is common, and the diameter of the lesions ranges from 3.0 to 12.0 cm. Infiltration below the deep fascia and into underlying bone is a feature. Patients with generalized disease present with 1 of 2 types of neoplastic involvement. In children, generalized lymphadenopathy with minimal or no systemic or cutaneous involvement is the rule. In adults, lesions are seen in lymph nodes and also in the mucous membranes (tonsils, gastrointestinal tract), viscera such as the heart and lungs, and the skeleton. The onset of disease is rapid and, if untreated, fatal within a few weeks.

Based on this clinical classification, Templeton and Bhana[27] provide the following prognostic conclusions.

1. Involvement of lymph nodes influences prognosis in that a poor prognosis is indicated in patients with generalized nodal involvement. Local nodal involvement in a patient with a locally aggressive tumor is a poor prognostic sign.
2. The age of the patient influences the type of disease likely to be present. However, the behavior of each clinical type of disease is the same, regardless of age.
3. The sex of the patient influences patterns of disease, with females manifesting generalized disease more often than males.
4. Dinitro-chlorobenzene testing is useful in patients with nodular disease, because those having a negative response have a significant risk of having systemic lesions, and in patients with aggressive lesions, because a negative response implies a poor prognosis.
5. Involvement of bone is a poor prognostic sign and is associated with aggressive tumors.

Hemangiopericytomas. Hemangiopericytomas are derived from pericytes. These lesions have fascinated clinicians and pathologists for more than 4 decades, despite the fact that they represent only

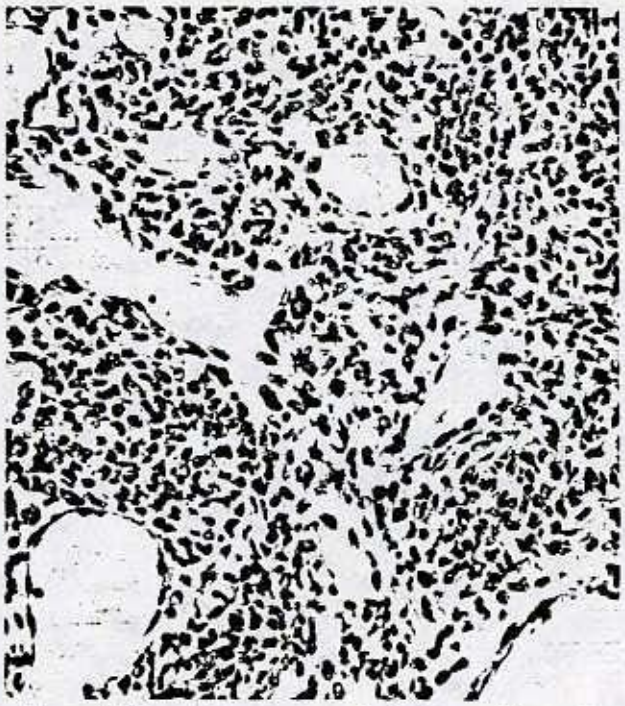

Figure 11. Hemangiopericytoma of soft tissues of the neck. This tumor is histologically low-grade. Note the perithelial location of the tumor cells. Hematoxylin and eosin, ×80.

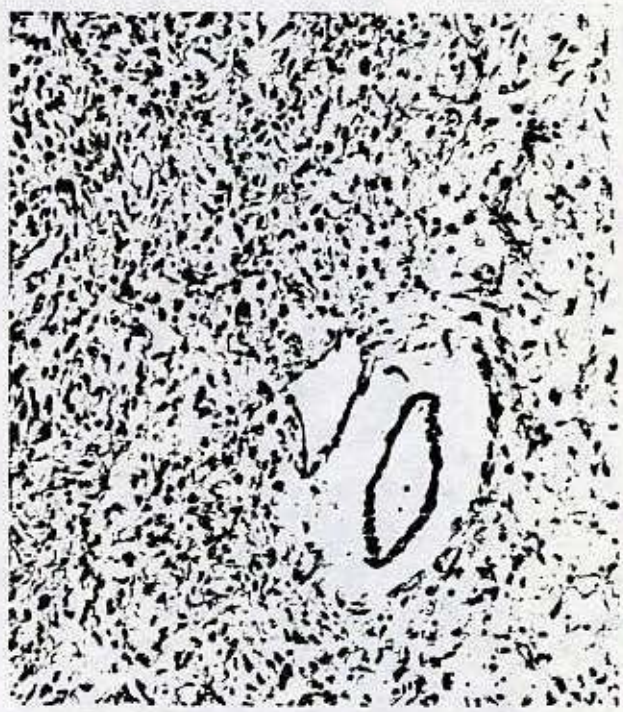

Figure 12. Hemangiopericytoma with secondary fibrosis and retrogressive changes in tumor cells. Hematoxylin and eosin, ×60.

1% of all vasoformative tumors. The incidence in the head and neck lies between 15% and 25% of all hemangiopericytomas. Most of these lesions arise in the soft tissues of the scalp, face, and neck. Origin in the oral cavity, nasal cavities, or paranasal sinuses is less common.

It is doubtful that hemangiopericytomas can be diagnosed preoperatively. Most of the tumors are grossly well circumscribed or even manifest a pseudocapsule. Some tumors may deceptively allow themselves to be easily removed. Their diameter ranges from less than 1 cm to more than 20 cm.[28] The tumors are solitary, their surface is lobulated or slightly nodular, and their consistency may be soft, spongy, firm, or friable, depending on the vascularity and stromal alterations. Except for a few dilated vascular spaces visible on gross inspection, there is no good clue to a vascular origin.

The basic microscopic pattern of hemangiopericytomas is one of vascular channels that range from gaping sinusoidal spaces to capillaries. Pericytes are oriented about the vascular spaces and outside the reticulin sheath of the endothelium, and they fill the spaces between the vessels (Fig. 11). The latter form a continuous ramifying vascular system with considerable variation in caliber. Enzinger and Smith[29] describe the tumor vasculature as a "vascular swamp" fed by radially disposed feeders from the pericapsular tissue. This description does little justice to the histologic variation that can occur. Some of the variation is brought about by fibrosis, interstitial mucoid changes, and focal necrosis (Fig. 12). The fibrosis may be diffuse or localized (perivascular). Necrosis, hemorrhage, and thrombotic vascular occlusion are observed chiefly in very cellular and presumably rapidly growing hemangiopericytomas.

The distinction between malignant and benign hemangiopericytomas is difficult or impossible to make, but certain features characterize the tumors that pursue an aggressive or malignant course. Gross features suggestive of malignancy are:

1. Tumor diameter greater than 6.5 cm.
2. Anatomic site (the retroperitoneum, extremities, and trunk are least favorable).
3. Recurrences.

Microscopic features suggestive of malignancy are:

1. Mitotic figures.
2. Cellular anaplasia and increased cellularity.
3. Necrosis.
4. Hemorrhage.

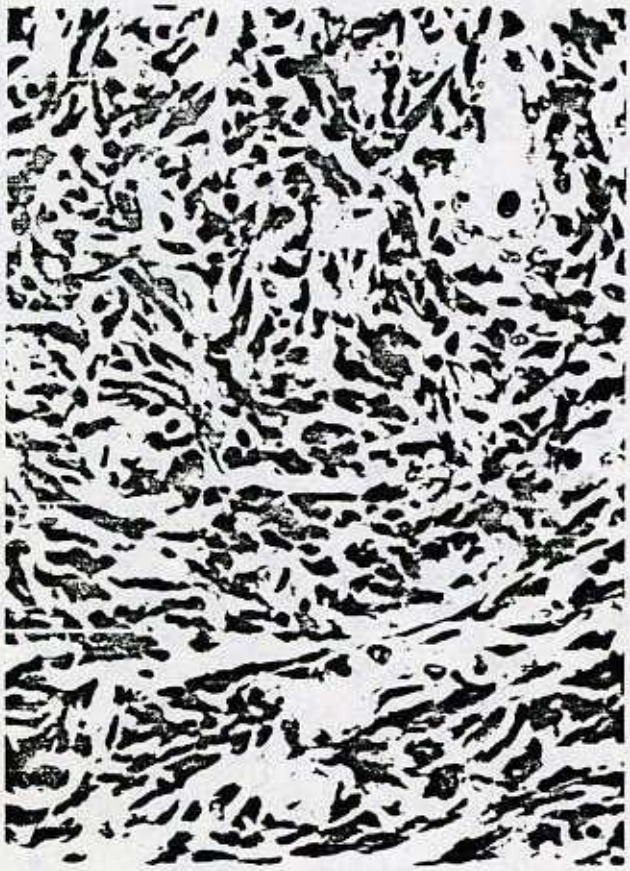

Figure 13. High-grade hemangiopericytoma. Tumor cells are spindle-shaped and hyperchromatic, and vascular spaces are difficult to find. Hematoxylin and eosin, ×150.

It is likely that a histologic grading system will evolve for these tumors as more clinicopathologic correlations are accumulated. The work of McMaster et al.[30] shows that some predictability can be achieved by categorizing the neoplasms as histologically benign (low-grade), histologically borderline (intermediate-grade), and histologically malignant (high-grade).

The low-grade hemangiopericytomas are those with a prominent vascular pattern and scant areas of compressed vascular spaces. The pericytes are primarily spindled in form with only foci of more plump cells. An absence of mitotic figures or no more than 1 per 20 high-power fields is typical. Necrosis and hemorrhage are absent.

Intermediate-grade hemangiopericytomas are more cellular, have a less prominent vascular pattern, and have more compression of vascular spaces than low-grade hemangiopericytomas. The tumor cells are more plump and less spindled. Mitoses are not numerous, but are more evident than in the low-grade lesions.

High-grade hemangiopericytomas are characterized by increased anaplasia, more mitoses, and more compression of the vascular spaces (Fig. 13).

Survival of patients is also less favorable if their hemangiopericytomas lack a lymphocytic infiltrate and show little fibrosis or desmoplasia.

Using such a grading system, McMaster et al.[30] found that all of their patients with low-grade hemangiopericytomas were free of disease after follow-up periods of more than 5 years (6 to 19 years). Of 16 patients with intermediate-grade hemangiopericytomas in their series, 6 died of metastases and 7 are alive and free of disease, 1 at 3 years and 6 at periods ranging from 10 to 22 years. Of 32 patients with high-grade malignancies, 23 died of metastatic disease. Metastases eventually developed in nearly 65% of patients considered to have malignant or borderline malignant hemangiopericytomas. The lungs and skeleton are the 2 principal sites of metastatic deposits.

Enzinger and Smith[29] correlated 10-year survival rates with the mitotic index of the tumors and with necrosis, hemorrhage, and size. For tumors with 0 to 3 mitotic figures per 10 high-power fields, the survival rate was 77%. This dropped to 29% for tumors with 4 or more mitotic figures per 10 high-power fields. The relative 10-year survival for patients who had tumors with necrosis was 81% and for those with tumors without necrosis it was 29%. Tumors larger than 6.5 cm were associated with a 10-year survival of 63%, whereas the survival with tumors smaller than 6.5 cm was 92%. Recurrence is also ominous for survival, as indicated by Enzinger and Smith,[29] who found that 11 of 16 recurrent tumors produced metastases at a later stage in the disease.

Recurrence, distant metastasis, and death are associated with hemangiopericytoma in a high percentage of patients (Tables 1–3).[28–34] Long-term follow-up is imperative because there may be recurrences after 5 "disease-free" years. Enzinger and Smith[29] record a median time of 17 months for recurrence (range 1 month to 7 years). They also cite a median interval from diagnosis to metastasis of 4½ years (range 1–14 years). The possibility of death due to the neoplasm extends throughout the natural life of a patient with a hemangiopericytoma. In some series, one-third to one-half of the patients died within the first 5 years after primary therapy. Other patients died in the next 5 to 20 years.

Hemangiopericytomas of the head and neck. While the foregoing data on the morbidity and mortality of hemangiopericytomas in general are

Table 1. Recurrence rates associated with hemangiopericytoma.*

Anatomic area	No. of cases with recurrence/total (%)	% with recurrences		
		0–1 yr	1–5 yrs	5 or more yrs
Orbit, oral cavity, nasal cavity, sinuses	12/21 (57)	4.7%	19%	33.3%
Muscle, skeleton, skin	52/103 (50.4)	11.6%	23.3%	15.5%
Abdomen (retroperitoneum, uterus)	16/39 (41)	2.5%	20.5%	18%

*Extracted from data presented by Backwinkel and Diddams.[31]

Table 2. Metastasis rates associated with hemangiopericytoma (all sites).

Study	No. of cases with metastases/total (%)
Gerner et al.[34]	7/13 (53.8)
McMaster et al.[30]	34/60 (56.7)
O'Brien and Brasfield[33]	13/23 (56.5)
Angervall et al.[28]	2/11 (18.2)
Fisher[32]	9/20 (45)

Table 3. Mortality rates associated with hemangiopericytoma (all sites).

Study	No. of patients who died/ total (%)	No. living with disease
Enzinger and Smith[29]	22/93 (23.6)	6
O'Brien and Brasfield[33]	11/23 (47.8)	2
McMaster et al.[30]	36/60 (60.0)	5
Gerner et al.[34]	7/13 (53.8)	2

impressive, it is difficult to extract significant data on the behavior of hemangiopericytomas of the head and neck. Many reports deal with single or small numbers of cases and often lack sufficient follow-up. For example, O'Brien and Brasfield[33] found a 5-year survival of 100% in 7 patients with head and neck hemangiopericytomas, but 4 of the 7 patients died later (after 8, 16, 18, and 21 years) after multiple recurrences.

When hemangiopericytomas from all anatomic sites are considered, a recurrence rate of 25%–50% and a metastasis rate of 12%–60% are seen. Hemangiopericytomas of the head and neck, including those arising in the upper air passages (Table 4), appear to behave in a less malignant fashion.[35-38] That the head and neck may be a site for less clinically aggressive hemangiopericytomas is suggested by data presented by Walike and Bailey[34] and Compagno and Hyams.[35] Walike and Bailey[34] reported that although 19 of their 43 patients manifested local recurrences, only 4 suffered metastases. A less aggressive biologic behavior is also indicated by Compagno and Hyams[35] for hemangiopericytomas arising in the nasal cavity and paranasal sinuses. Other authors, dealing with fewer patients, have also observed this difference in behavior. Data on 48 cases from the literature add credence to this possibility (Table 5).[35-37] Except for the cases in the Armed Forces Institute of Pathology series,[35] the rate of recurrence is in accord with that of hemangiopericytomas of other sites.[35,39]

Reasons for the apparent difference in biologic behavior are not at hand. The nasal cavity and paranasal sinuses are not usually favorable sites for supporting tissue neoplasms. It is possible that these regions favor the histogenesis of histologically low-grade hemangiopericytomas. Indeed, high-grade, anaplastic hemangiopericytomas are unusual or rare in the nasal cavity and sinuses. Judging from descriptions and photomicrographs, most of the hemangiopericytomas possess the features associated with benign behavior. The tumors of Compagno and Hyams[35] showed little nuclear or cytoplasmic pleomorphism, minimal or no mitotic activity, no necrosis, no hemorrhage, and no other evidence of anaplasia associated with biologically malignant hemangiopericytomas (Figs. 14 and 15). In fact, the authors were so impressed with the uniformity of cellular pattern that they qualified their diagnoses to "hemangiopericytoma-like."

The oral cavity, oropharynx, parapharyngeal soft tissues, and larynx have also been reported as primary sites.[40] In the oral cavity, the tumors have arisen from the tongue (including the base), the buccal sulcus, the gingiva, and the floor of the mouth.

Table 4. Locations of hemangiopericytomas of the nasal cavity and paranasal sinuses.

Study	No. of cases			
	Sphenoethmoid and ethmoid region	Nasal cavity	Nasopharynx	Maxillary region
Walike and Bailey[38]	2	5	1	3
Gorenstein et al.[36]	1	8	1	—
Compagno and Hyams[35]	10	13	—	—
Total	13	26	2	3

Table 5. Biologic behavior of hemangiopericytomas of the nasal cavity and paranasal sinuses.

Study	No. of cases	No. with recurrences	No. with metastasis	No. dead of disease
Gorenstein et al.[36]	10	3	1[a]	1
Güdrún[37]	15	8	1	1 (?)
Compagno and Hyams[35]	23	2	0	0

[a]*Cervical nodes and lungs.*

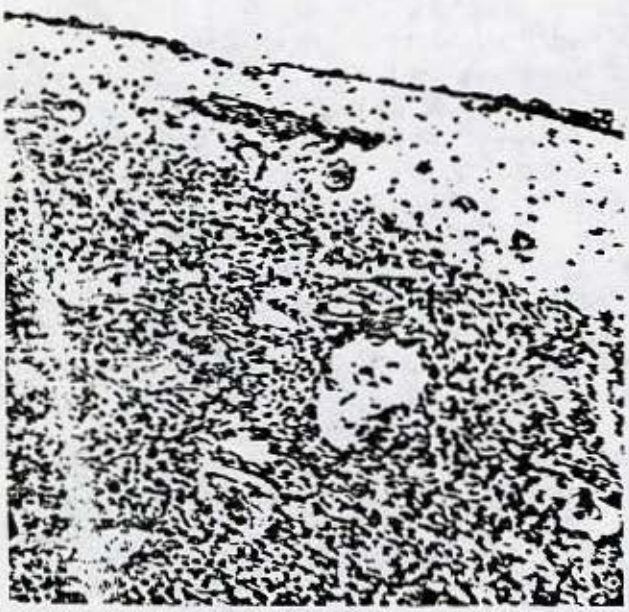

Figure 14. Hemangiopericytoma of nasal cavity. Cells are uniform and there is a prominent perivascular hyaline cuffing. Hematoxylin and eosin, ×50.

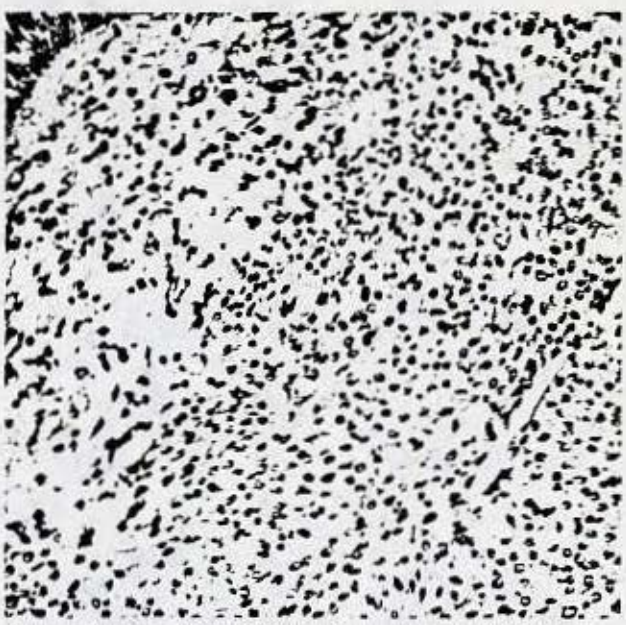

Figure 15. Hemangiopericytoma of nasal cavity. Perivascular hyaline is again seen. The pericytes in this lesion are uniform and bland in appearance and have an epithelial character. Hematoxylin and eosin, ×60.

Although hemangiopericytomas of the head and neck seem to offer a better outlook as far as metastases are concerned, recurrences are still a problem for the head and neck surgeon. These may be locally extensive and destructive or even fatal. A difference in biologic behavior between head and neck hemangiopericytomas and hemangiopericytomas of other sites can only be established after documentation with more cases and prolonged surveillance of patients.

Infantile or congenital hemangiopericytoma. The infantile or congenital hemangiopericytoma merits special mention as a specific clinicopathologic entity for several reasons.[29] It occurs almost exclusively during the years of infancy, presents exclusively in the subcutis, and has a predilection for the head and neck. In addition, despite histologic findings equated with malignancy in adult hemangiopericytomas (mitoses, necrosis, hemorrhage, increased cellularity, and perivascular and intravascular growth), the tumors follow a benign course in infants.

Microscopically, the tumors differ from the conventional hemangiopericytoma by a more pronounced acidophilic collagenous matrix, an irregular distribution of the vascular pattern, and proliferation of endothelial cells into the lumens of the vascular spaces. Necrosis, mitoses, and hemorrhage are common. The endothelial proliferation points to a relationship with the cellular hemangiomas of infancy.

That the benign course of this distinctive hemangiopericytoma does not apply to all hemangiopericytomas of the head and neck in childhood is underscored by the estimate of Kauffman and Stout[41] of a 35% malignancy rate in that age group.

Ultrastructural studies of hemangiopericytomas have been somewhat controversial, very likely reflecting the variations and differences in development of the constituent cells. They do, however, support the pericytic origin of hemangiopericytoma.[42,43] Transitional forms between pericytes and endothelial cells are also common in adult and infantile hemangiopericytomas and in cellular infantile or congenital hemangiomas,[43] a finding that suggests a close histogenetic relationship between these lesions.

SUMMARY

A clinicopathologic review of vasoformative tumors of the head and neck has been presented. These tumors may be as innocuous as pyogenic granulomas and resolving congenital hemangiomas or carry a considerable morbidity and mortality as manifested by hemangiopericytomas and angiosarcomas. Tumors of the lymphatic vascular system parallel the blood vascular lesions except for an absence of definable lymphangiosarcomas in the head and neck. The next offering in the series on pathology of tumors of the head and neck will deal with occult primary and other metastases to the head and neck.

REFERENCES

1. Angelopoulos AP: Pyogenic granuloma of the oral cavity: statistical analysis of its clinical features. *J Oral Surg* 29:840–847, 1971
2. Ash JE, Old JW: Hemangiomas of the nasal septum. *Trans Am Acad Ophthalmol Otolaryngol* 54:350–356, 1950
3. Kent DL, Fitzwater JE: Nasal hemangioma of pregnancy. *Ann Otol* 88:331–333, 1979
4. McClatchey KD, Batsakis JG, Young SK: Intravascular angiomatosis. *Oral Surg* 46:70–73, 1978
5. Cooper PH, McAllister HA, Helwig EB: Intravenous pyogenic granuloma. A study of 18 cases. *Am J Surg Pathol* 3:221–228, 1979
6. Clearkin KP, Enzinger FM: Intravascular papillary endothelial hyperplasia. *Arch Pathol Lab Med* 100:441–444, 1976
7. Kohout E, Stout AP: The glomus tumor in children. *Cancer* 14:555–565, 1961
8. Stout AP: Tumors featuring pericytes: glomus tumor and hemangiopericytoma. *Lab Invest* 5:217–223, 1956
9. Shugart RR, Soule EH, Johnson EW Jr: Glomus tumor. *Surg Gynecol Obstet* 117:334–340, 1963
10. Pepper MC, Laubenheimer R, Cripps DJ: Multiple glomus tumors. *J Cutan Pathol* 4:244–257, 1977
11. Girard C, Johnson WC, Graham JH: Cutaneous angiosarcoma. *Cancer* 26:868–883, 1970
12. Bardwil JM, Mocega EE, Butler JJ, Russin DJ: Angiosarcomas of the head and neck region. *Am J Surg* 116:548–553, 1968
13. Farr HW, Carandang CM, Huvos AG: Malignant vascular tumors of the head and neck. *Am J Surg* 120:501–504, 1970
14. Hodgkinson DJ, Soule EH, Woods JE: Cutaneous angiosarcoma of the head and neck. *Cancer* 44:1106–1113, 1979
15. Dabska M: Malignant endovascular papillary angioendothelioma of the skin in childhood. Clinicopathologic study of 6 cases. *Cancer* 24:503–510, 1969
16. Bankaci M, Myers EN, Barnes L, DuBois P: Angiosarcoma of maxillary sinus: literature review and case report. *Head Neck Surg* 1:274–280, 1979
17. Sharma BG, Mawalkha PL: Angiosarcoma of the maxillary antrum: report of a case with brief review of literature. *J Laryngol* 93:181–186, 1979
18. Rosai J, Sumner HW, Kostianovsky M, Perez-Mesa C: Angiosarcoma of the skin. A clinicopathologic and fine structural study. *Hum Pathol* 7:83–109, 1976
19. Dahlin DC: Vascular tumors. In *Bone Tumors*, 2nd Ed. Charles C Thomas, Springfield, IL, 1967, p 100

20. Larsson SE, Lorentzon R, Boquist L: Malignant hemangioendothelioma of bone. *J Bone Joint Surg* [Am] 57:84–89, 1975
21. Bundens WD Jr, Brighton CT: Malignant hemangioendothelioma of bone. Report of two cases and review of the literature. *J Bone Joint Surg* [Am] 47:762–772, 1965
22. Unni KK, Ivins JC, Beabout JW, Dahlin DC: Hemangioma, hemangiopericytoma, and hemangioendothelioma (angiosarcoma) of bone. *Cancer* 27:1403–1414, 1971
23. Garcia-Moral CA: Malignant hemangioendothelioma of bone. Review of world literature and report of two cases. *Clin Orthop* 82:70–79, 1972
24. Warner TF, O'Loughlin S: Kaposi's sarcoma: a byproduct of tumour rejection. *Lancet* ii:687–689, 1975
25. Abramson AL, Simons RL: Kaposi's sarcoma of the head and neck. *Arch Otolaryngol* 92:505–507, 1970
26. O'Connell KM: Kaposi's sarcoma: histopathological study of 159 cases from Malawi. *J Clin Pathol* 30:687–695, 1977
27. Templeton AC, Bhana D: Prognosis in Kaposi's sarcoma. *J Natl Cancer Inst* 55:1301–1304, 1975
28. Angervall L, Kindblom LG, Nielsen JM, Stener B, Svendsen P: Hemangiopericytoma: a clinicopathologic, angiographic and microangiographic study. *Cancer* 42:2412–2427, 1978
29. Enzinger FM, Smith BH: Hemangiopericytoma. An analysis of 106 cases. *Hum Pathol* 7:61–82, 1976
30. McMaster MJ, Soule EH, Ivins JC: Hemangiopericytoma. A clinicopathologic study and long-term followup of 60 patients. *Cancer* 36:2232–2244, 1975
31. Backwinkel KD, Diddams JA: Hemangiopericytoma: report of a case and comprehensive review of the literature. *Cancer* 25:896–901, 1970
32. Fisher JH: Hemangiopericytoma: a review of 20 cases. *Can Med Assoc J* 83:1136–1139, 1960
33. O'Brien P, Brasfield RD: Hemangiopericytoma. *Cancer* 18:249–252, 1965
34. Gerner RE, Moore GE, Pickren JW: Hemangiopericytoma. *Ann Surg* 179:128–132, 1974
35. Compagno J, Hyams VJ: Hemangiopericytoma-like intranasal tumors. A clinicopathologic study of 23 cases. *Am J Clin Pathol* 66:672–683, 1976
36. Gorenstein A, Facer GW, Weiland LH: Hemangiopericytoma of the nasal cavity. *Otolaryngology* 86:405–415, 1978
37. Güdrün R: Haemangiopericytoma in otolaryngology. *J Laryngol Otol* 93:477–494, 1979
38. Walike JW, Bailey BJ: Head and neck hemangiopericytoma. *Arch Otolaryngol* 93:345–353, 1971
39. Compagno J: Hemangiopericytoma-like tumors of the nasal cavity: a comparison with hemangiopericytoma of soft tissues. *Laryngoscope* 88:460–469, 1978
40. Ferlito A: Primary malignant haemangiopericytoma of the larynx. (A case report with autopsy). *J Laryngol* 92:511–519, 1978
41. Kauffman SL, Stout AP: Hemangiopericytoma in children. *Cancer* 13:695–710, 1960
42. Battifora H: Hemangiopericytoma: ultrastructural study of five cases. *Cancer* 31:1418–1432, 1973
43. Taxy JB, Gray SR: Cellular angiomas of infancy. An ultrastructural study of two cases. *Cancer* 42:2322-2331, 1979

Case 12. Mandible, chondrosarcoma (low-grade)

Cartilage tumors in the head and neck are always highly suspect for chondrosarcoma. Even if histologic criteria are not satisfied, those of the maxilla and mandible are locally aggressive. A diagnosis of chondroma is one made with complete discussion with the surgeon because of the potential biologic course in the gnathic bones.

Nearly all of the mandibular or maxillary chondrosarcomas are low-grade histologically. The M. D. Anderson files contain only one example of de-differentiated mandibular chondrosarcoma.

Care should always be taken to exclude a chondroblastic osteogenic sarcoma because of the much higher morbidity of osteosarcomas.

The facial soft tissues and bones are also sites of predilection for mesenchymal chondrosarcomas, lesions which may, in areas, resemble hemangiopericytomas or synovial sarcomas.

The accompanying reprint summarizes the cartilaginous tumors of the head and neck and compares them to osteogenic sarcomas and tumors of the notochord—chordomas.

THE PATHOLOGY OF HEAD AND NECK TUMORS: NEOPLASMS OF CARTILAGE, BONE, AND THE NOTOCHORD, PART 7

JOHN G. BATSAKIS, MD, ALVIN R. SOLOMON, MD, and DALE H. RICE, MD

Abstract: Neoplasms of the supporting tissues in the head and neck are outnumbered by their histologic counterparts in the trunk and extremities. This is especially true for tumors of bone, cartilage, and the remnants of the notochord. Malignancies occurring in all three tissues, however, are just as lethal as those sited elsewhere. Chondrosarcomas and osteogenic sarcomas of the facial bones are resistant to all conventional modes of therapy, manifest many recurrences, and have an often protracted morbidity. The craniocervical chordoma manifests a similar biologic course. For the tumors of cartilaginous origin and the osteogenic sarcomas, the initial surgical attempt at removal is of key importance. Neoplasms present at the margins of resection have a poor prognosis. Chordomas are not likely to be cured by any modality.

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Cartilage, bone, and remnants of the notochord yield neoplastic disorders of low incidence in the head and neck. The infrequent occurrence and the difficulties of histopathologic diagnosis inherent in these groups of neoplasms provide some of the greatest challenges to the surgical pathologist and head and neck surgeon. In this review, we will present only the major neoplastic growths of these supporting tissues and briefly address some of the benign disorders bearing on differential diagnosis or having implications for pathogenesis of the neoplasms.

CARTILAGINOUS TUMORS

The majority of cartilage-derived neoplasms in the head and neck behave in a malignant or locally aggressive manner.

Many lesions containing cartilage are classified as chondromas. Included in this category are lesions such as cartilaginous spurs of the nasal septum and osteochondromas, although the latter are more appropriately regarded as exostoses. The exostoses exist in solitary or multiple forms and are usually clinically silent. The solitary tumor is rarely premalignant, but the incidence of complicating chondrosarcoma in patients with multiple osteochondromas is significant.[36] The relationship of the osteochondroma to benign cartilage tumors, i.e., chondromas, is remote. Chondromas also exist in multiple and solitary forms and may be either central (endosteal) or peripheral.

We view all cartilaginous neoplasms of the jaws and facial skeleton with suspicion and a

Table 1. Sites of origin of chondromas of the nose and paranasal sinuses.

Site of origin	Percentage*
Ethmoid region and nasal cavity	50
Septum	17
Maxilla and maxillary antrum	18
Hard palate	6
Nasopharynx, sphenoid sinus, or eustachian tube	6
Alar cartilages	3

*Patient population = 135, selected from Chaudhry et al.,[7] Fu and Perzin,[14] Kilby and Ambegaokar,[19] and Roca et al.[29]

Table 2. Incidence of chondrosarcoma of the jaws in the maxilla and mandible.*

Reference	Maxilla	Mandible
Arlen et al[1]	10	4
Kragh et al[22]	2	0
Chaudhry et al[7]	21	15
Sato et al[30]	12	10
Total	45	29

*Data (given as the number of cases) are selected from series clearly identifying the maxilla or mandible as the primary site.

great deal of respect. In so doing, we assume the following: (*a*) all so-called chondromas proximal to the hands and feet are suspect for malignancy, (*b*) multiple blocks from cartilaginous tumors should be examined because areas diagnostic of a chondrosarcoma may be only focal, (*c*) the size of a cartilaginous tumor may be a final determinant with 3.0 cm being the maximum size expected of a chondroma, (*d*) dedifferentiation of a benign or low-grade cartilaginous tumor is always possible, and (*e*) an adequate margin of normal tissue is mandatory for all cartilaginous tumors.

The histopathologic distinction between a chondroma and a histologically low-grade chondrosarcoma is notoriously difficult to make. Many of the fine structural features of low-grade chondrosarcoma cells are also found in cells of normal hyaline cartilage. Erlandson and Huvos[10] have stated: "one would be hard pressed to point out differences between normal chondrocytes and neoplastic cartilage cells in low grade chondrosarcomas." As may be expected, there are also few histochemical differences between benign cartilage and low-grade chondrosarcoma.[20] This underscores the problems that the pathologist must deal with on encountering a cartilage-derived tumor in the head and neck. Lack of sufficient follow-up for many so-called chondromas further hampers prognostication.

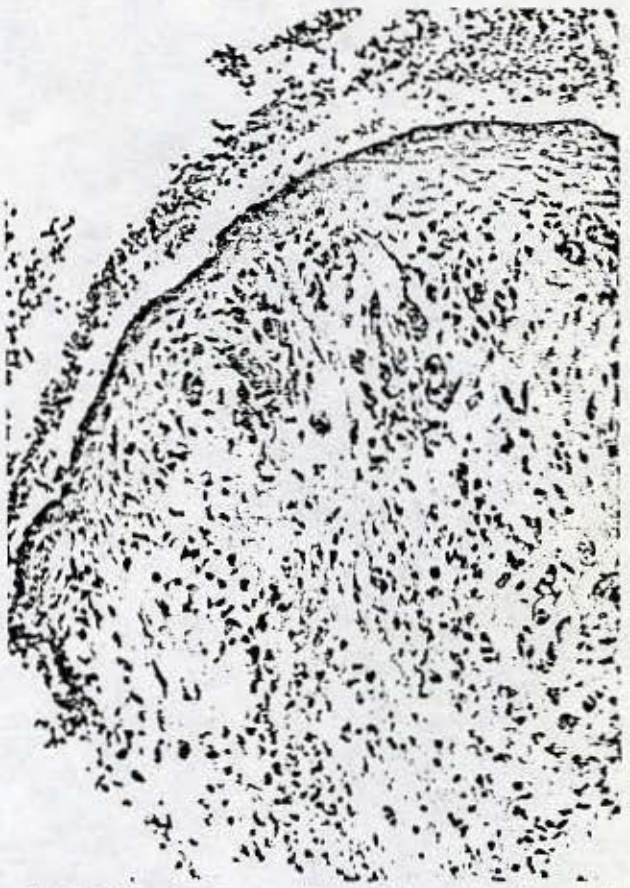

Figure 1. Chondrosarcoma of the maxilla pushing attenuated mucosa. Hematoxylin and eosin, ×60.

Chondromas in the head and neck have been reported most often to occur in regions other than the maxilla and mandible, illustrating once again the suspect nature of cartilage tumors in those sites. Table 1 lists the sites of origin of 135 chondromas of the nasal cavity and paranasal sinuses.[7,14,19,29]

Chondrosarcomas of the jaws and maxillofacial skeleton are uncommon. Kragh et al[22] cited 10 cases from the Mayo Clinic files over a 50-year period, and Evans et al[11] reported only 18 chondrosarcomas of the head and neck (excluding the larynx) at Memorial Hospital (New York, NY) from 1932 through 1968. The Japanese literature contained only 35 cases reported in a 50-year period.[30] An estimate of the incidence of chondrosarcomas of the jaws would be 1.25% of all chondrosarcomas in the body.

Despite this relatively small experience, certain demographics of the malignancy can be derived. Chondrosarcomas of the maxilla occur more frequently than those of the mandible (table 2). The occurrence of chondrosarcomas is almost

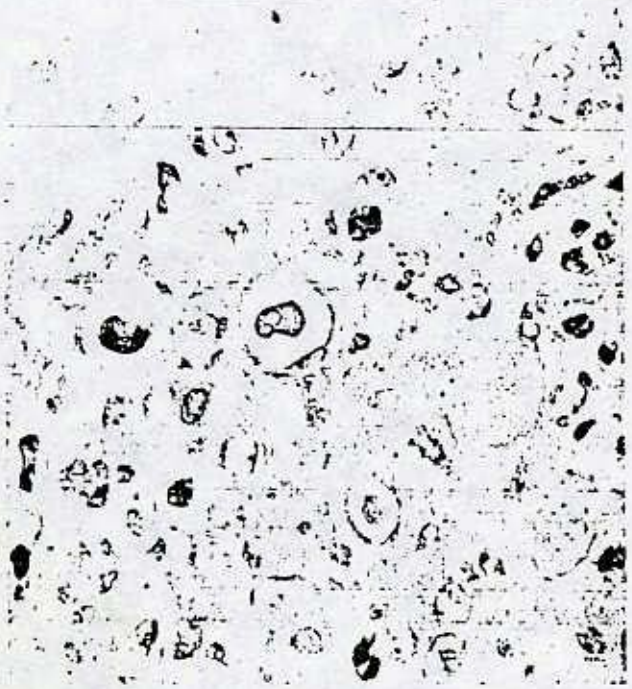

Figure 2. Chondrosarcoma of the maxilla manifesting cell clusters, large nuclei, and atypical forms. Hematoxylin and eosin, ×140.

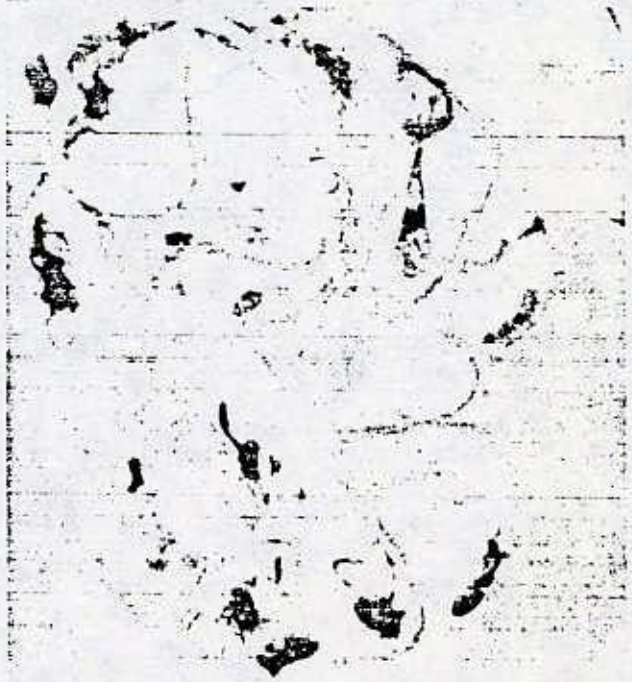

Figure 3. Bizarre nuclei in a chondrosarcoma of the mandible. Hematoxylin and eosin, ×220.

equal in men and women; there is a tendency, however, for women to manifest more maxillary than mandibular chondrosarcomas. Chondrosarcomas of extrafacial sites have a peak incidence in the sixth decade. The average age of the host for chondrosarcomas of the jaw bone is about 60 years, with nearly half of the reported examples occurring during the third and fourth decades. The most common sites of chondrosarcomas of the maxilla are the anterior area, the palate, and the vicinity of the lateral incisors and canine teeth (fig. 1). When the origin is in the mandible, the sites of predilection are the premolar and molar regions, the symphysis, and the coronoid and condylar processes.

Radiology shows chondrosarcomas to be destructive lesions with single or multiple radiolucent areas. Mottled calcification may be present. Chondrosarcomas and osteogenic sarcomas share a uniform widening of the periodontal membrane space.

The preference for chondrosarcomas to arise from specific areas of the mandible and maxilla has given rise to speculations concerning the tissues of origin in the jaws.[25] Assumed, but not proven, is origin from vestigial rests and proximity of the anterior region of the maxilla to the premaxilla and cartilaginous nasal capsule. The posterior part of the mandible is related to possible remnants of Meckel's cartilage. Other sites of origin are areas of chondroid bone found in the alveolar ridges and mandibular angles, and mesenchymal cells with the potential to differentiate into chondroblasts.

The most common clinical signs of a chondrosarcoma of the jaw bones are swelling, expansion of the buccal and lingual plates, and premature eruption or exfoliation of teeth. Pain, trismus, neural sensory deficits, and nasal signs indicate extension of the neoplasms. Duration of symptoms before the patient seeks medical advice usually averages less than a year.

Light microscopic features for the diagnosis of chondrosarcoma include increased numbers of cartilage cells with plump nuclei, more than occasional binucleate cells, and the presence of multinucleated giant cartilage cells (figs. 2 and 3).

A system having prognostic significance is cytologic grading of chondrosarcomas.[10,11] Grade 1 tumors manifest cystic and myxomatous changes and have a preponderance of small, dense nuclei. Calcification and bone formation are frequent, but not unique, features of low-grade chondrosarcomas. An increased cellularity, particularly at the periphery of the neoplastic lobules, is characteristic of grade 2 chondrosarcomas (fig. 4).

Figure 4. Hypercellularity, atypical cells, and mitoses, characteristic of grade 2 chondrosarcomas, in a microscopic field from a chondrosarcoma of the maxilla. Hematoxylin and eosin, ×100.

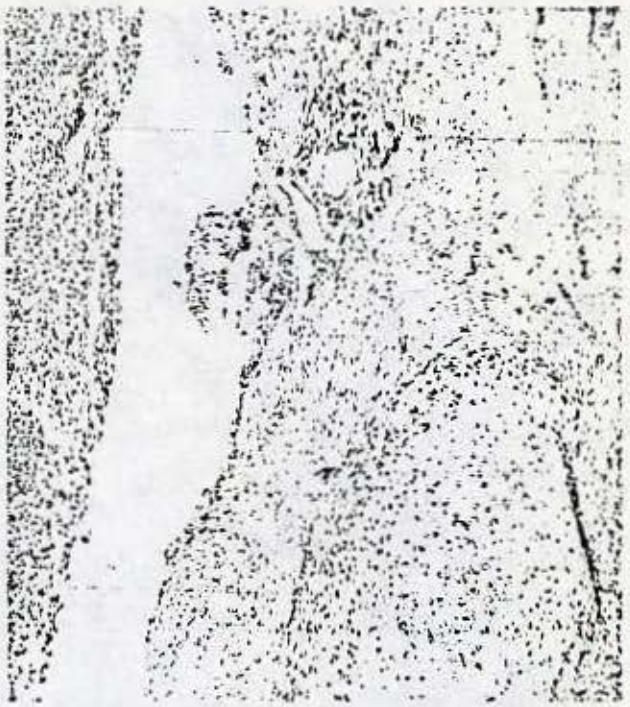

Figure 5. Chondrosarcoma of the maxilla (lower right) extending into the cranial vault and adjacent to the pituitary gland (left). Hematoxylin and eosin, ×40.

Mitoses (less than 2 per 10 high-power fields) are present. The increased number of cells and greater size of the cell nuclei that are characteristic of this grade of chondrosarcoma may be limited in scope, and the remainder of the tumor may look like a grade 1 chondrosarcoma. Grade 3 chondrosarcomas have a pronounced cellularity, a mitotic rate of 2 or more per 10 high-power fields, and a spindle formation of the cells. Correlation of the three grades also exists at the ultrastructural level.

Dedifferentiation in benign cartilage tumors or low-grade chondrosarcomas may be expected in approximately 10% of those lesions.[10,11] In this event, the resulting malignancy is one with a combination of well-differentiated or "borderline" chondrosarcomas in juxtaposition to areas of an anaplastic fibrosarcoma or osteogenic sarcoma. Dedifferentiated chondrosarcomas have site predilections for tubular bones and the innominate bones.

The prognosis of any chondrosarcoma is dependent upon three factors: (*a*) the location of the primary lesion, (*b*) the adequacy of surgical removal of the primary lesion, and (*c*) the histologic grade of the neoplasm. Of these three factors, the first two are predominant.

Patients with chondrosarcoma involving the facial bones, nasal cavity, and sinuses usually have a slow, progressive course of their disease, and many may survive for prolonged periods with multiple recurrence. Death results from uncontrolled local disease and extension to the base of the skull and into the cranial cavity (fig. 5). Distant metastases are a constant threat, especially to the patient with multiple recurrences, but occur infrequently.[8] Fu and Perzin[14] give an incidence of 8%.

Five-year survival statistics only tell a partial story since death may occur after that interval. Fu and Perzin[14] record a 5-year survival of 62%, and Kragh et al[22] a 5-year survival of 40%, compared with a 5-year rate of 54% for chondrosarcomas of extrafacial sites.[18] The mandible appears to harbor a more deadly chondrosarcoma than the maxilla.

At the present time, radical resection is the only treatment offering a significant chance for cure. Prognosis improves almost in direct relationship to the width of margin of normal tissue encompassed by the surgical resection. Fu and Perzin[14] indicate that the only lesions to recur are those in which the neoplasm has extended to the lines of excision.

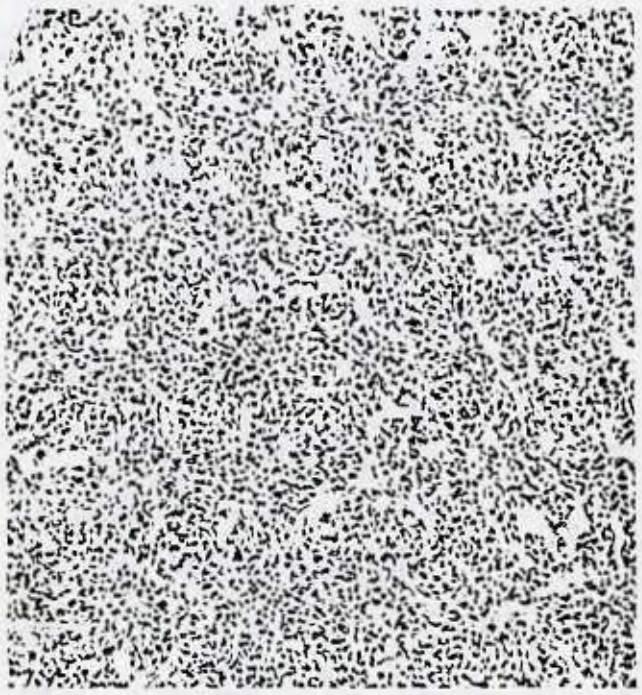

Figure 6. Mesenchymal chondrosarcoma of the maxilla. The undifferentiated precartilage cells tend to be arranged in a perivascular fashion and mimic a hemangiopericytoma. Hematoxylin and eosin, ×30.

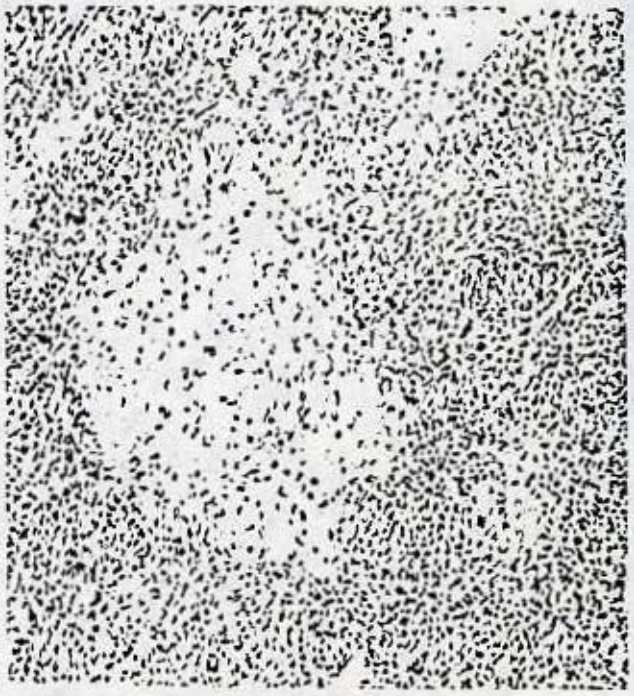

Figure 7. Mesenchymal chondrosarcoma with diagnostic islands of cartilage. Hematoxylin and eosin, ×40.

Mesenchymal Chondrosarcoma. This neoplasm is a distinctive type of chondrosarcoma that exists in both skeletal and extraskeletal forms. The lesion has a predilection for the facial bones and ribs and rarely affects tubular bones. More than one third of the reported examples have been in soft tissues, with the head and neck region (principally, the orbit) being the typical site of involvement.[5]

Histologic diagnosis of this lesion is established by the finding of a richly cellular neoplasm composed of undifferentiated mesenchymal cells, in which islands of relatively well-differentiated cartilage are found. The presence of this cartilage is essential to the diagnosis. Failure to find the foci of cartilage often leads to a misdiagnosis of hemangiopericytoma (figs. 6,7, and 8).

The tumor requires radical surgical removal. Excision, radiation, or curettage leads to a nearly predictable recurrence or, worse, metastasis and death. Metastases may appear after long periods of latency. A hematogenous spread, primarily to the lungs, is favored over lymphatic dissemination.

Extraosseous (nonmesenchymal) chondrosarcomas of the jaws occur rarely.[16] They originate from periosteal connective tissue elements that have differentiated into chondroblasts.

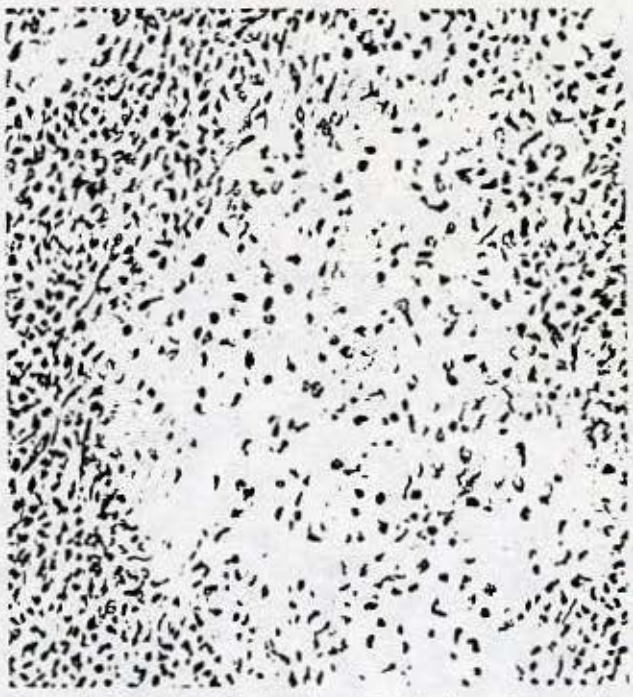

Figure 8. Mesenchymal chondrosarcoma in figure 7 at a higher magnification. Note the rather characteristic abruptness of the cartilage in the undifferentiated cell matrix. Hematoxylin and eosin, ×140.

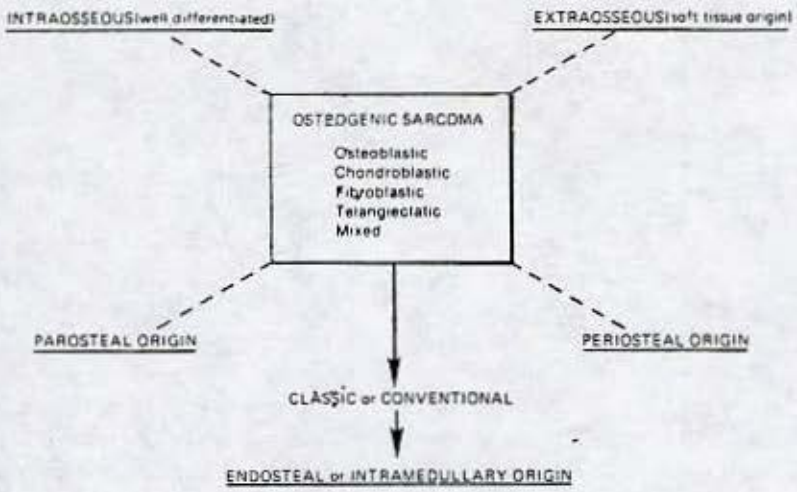

Figure 9. Histopathologic types and origins of osteogenic sarcoma.

Synovial Chondromatosis. All forms of tumor of the temporomandibular joint and condyle of the mandible must be considered rare. Cartilage-derived tumors appear to be especially unusual. Synovial chondromatosis and chondrosarcomas are equally rare, and this rarity along with unusual histologic features and general unfamiliarity on the part of surgical pathologists can lead to an overestimation of the biologic behavior of synovial chondromatosis.

Synovial chondromatosis is generally a monoarticular disease in which metaplastic islands of cartilage are formed within the synovium.[2] These islands grow into cartilaginous capsular bodies and, through friction and pressure, may become dislodged into the joint space to become free bodies. Once cartilage formation has been initiated, an increase in size occurs. This results from multiplication of the cartilage cells rather than from an accretion of cartilage. The nodules often become calcified or ossified, and may be highly cellular and manifest atypia. However, the formation of loose bodies within the capsule of the joint is not diagnostic of synovial chondromatosis because various forms of degenerative disorders of the joint or periarticular bone can also produce such bodies.

Synovial chondromatosis of the temporomandibular joint presents clinically with preauricular swelling and limited motion of the joint with deviation of the mandible to the affected side on opening the jaw. Pain may be associated with movement of the mandible.

Radiographic examination may reveal nothing or, occasionally, show radiopaque bodies within the synovium or as loose forms confined to the area of the joint capsule. Destruction of adjacent bone is not found.

Synovectomy and removal of the loose bodies result in cure. The superimposition of malignancy (chondrosarcoma) is unusual.[2,26]

OSTEOGENIC SARCOMA

Osteogenic sarcoma is a malignant neoplasm arising in bone or soft tissues in which the proliferating malignant cells produce osteoid substance. Osteoid, chondroid, or fibrous differentiation may predominate and thus yield osteoblastic, chondroblastic, and fibroblastic types of osteogenic sarcoma. The osteogenic sarcomas are classically endosteal or medullary, and then parosteal, periosteal, or extraosseous (fig. 9).

While osteogenic sarcoma is the most common primary malignant neoplasm of the bone, it is relatively rare in the oral and facial bone regions (table 3). Approximately 6.5% of all osteogenic sarcomas are primary in the jaws,[15] based on an incidence in the United States population of 0.07 per 100,000 per year.[15]

Osteogenic sarcomas of the long bones occur most frequently during the second decade of life. In contrast, the highest reported incidence of osteogenic sarcoma in the skull and jaw bones is in

Table 3. Incidence of osteogenic sarcoma of the jaws in the maxilla and mandible *

Reference	Maxilla	Mandible
Roca et al[29]	9	11
Finkelstein[13]	12	12
Garrington et al[15]	18	38
Kragh et al[21]	23	19
Caron et al[6]	15	17
Total	77	97

*Data represent the number of cases.

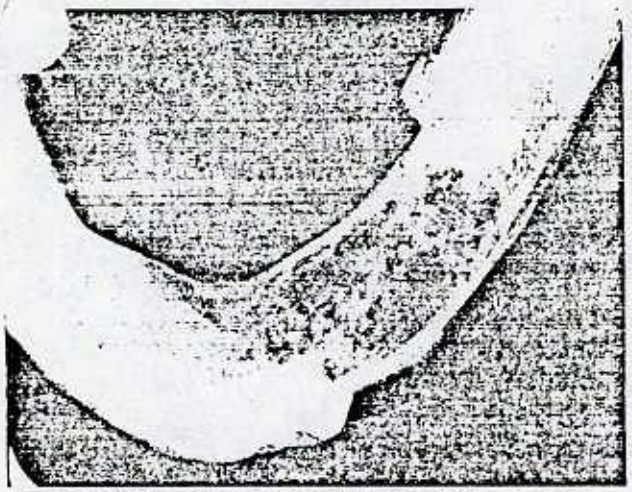

Figure 10. Osteogenic sarcoma of the mandible presenting as a predominantly lytic tumor.

the third decade (excluding patients who develop their sarcoma in Paget's disease of bone).[20] Among children, osteogenic sarcoma is the most frequent primary malignancy of the maxilla and mandible.

The radiologic features of osteogenic sarcoma depend largely on the state of ossification and mineralization in the tumor (fig. 10), ranging from completely lytic to totally sclerotic, with the majority having a mixture of both features. Destruction of the cortical plates as well as interruption of the inferior alveolar canal may be seen in advanced cases. In the early stages of jaw lesions, the apparent loss of the lamina dura and a uniform thickening of the periodontal ligament space may be the only signs present.

When the tumor penetrates the cortex, a florid periosteal reaction usually occurs with prominent soft tissue masses extending out from the tumor site. The periosteal reaction is characteristically interrupted and multilayered, often exhibiting either a radial "sunburst" or a laminated "onion-peel" appearance.

There is no symptom complex that is characteristic for osteogenic sarcoma of the facial bones. The most common presenting complaint is a painful swelling which often leads the patient to see his dentist. In the series presented by Caron et al,[6] almost half of the patients had extraction of teeth as their "primary" treatment. Encroachment into the nasal cavity and paranasal sinuses yields signs and symptoms related to obstruction of those spaces.

The gross appearance of osteogenic sarcoma is very dependent on the microscopic character, i.e., the degree of osteoblastic, fibroblastic, or chondroblastic proliferation. Hence, the tumors may be firm, gritty, granular, fleshy, or fibrous.

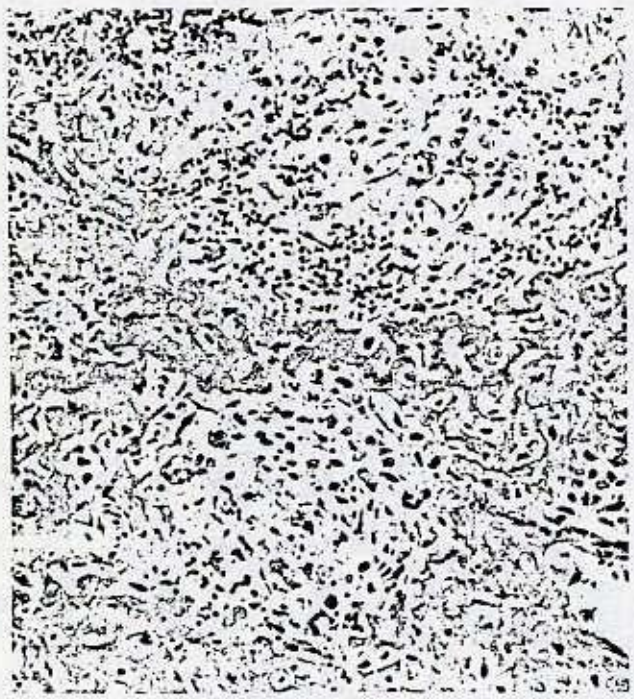

Figure 11. Sclerosing osteogenic sarcoma of the mandible. Hematoxylin and eosin, ×50.

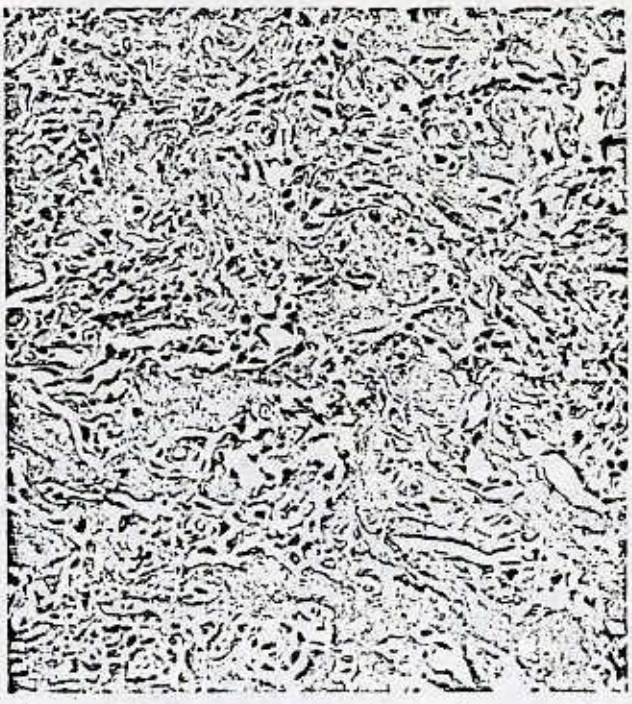

Figure 12. Sclerosing osteogenic sarcoma of the mandible. Hematoxylin and eosin, ×40.

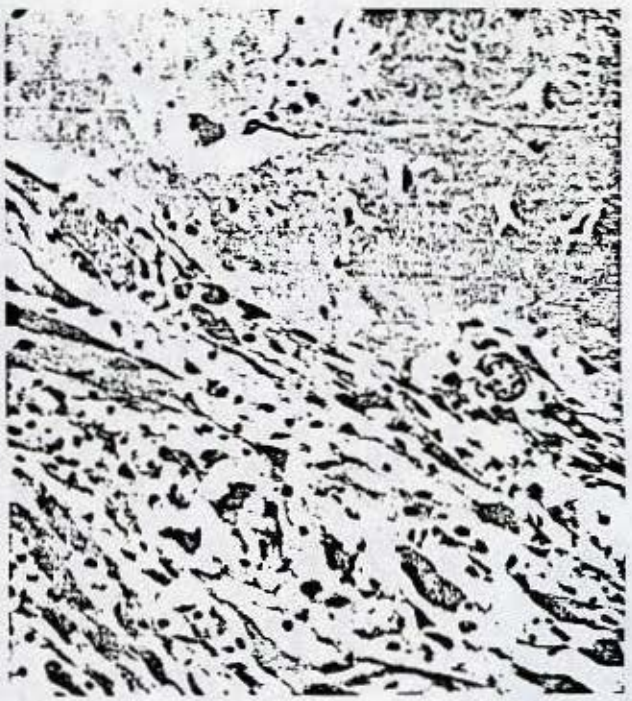

Figure 13. Osteogenic sarcoma of the mandible. Osteoid is present in the upper right. Sarcoma cells without osteoid formation lie in a vascular stroma below the osteoid. Hematoxylin and eosin, ×200.

Figure 14. Fibroblastic osteogenic sarcoma of the maxilla. Hematoxylin and eosin, ×180.

From a microscopic standpoint, osteogenic sarcomas of the jaws do not differ significantly from those of the long bones. In our experience and that of Caron et al,[6] the majority of the endosteal osteogenic sarcomas of the mandible are predominantly osteoblastic and sclerosing (see figs. 11–13).

In the maxilla, the sarcomas occasionally manifest a marked vascular and cellular pattern (figs. 14–16).

Local recurrences and distant metastases are the bane of the surgeon attempting to salvage patients with osteogenic sarcoma of the jaws. As expected, recurrences are more frequent with osteogenic sarcomas involving the maxilla, e.g., 80% in the series of Caron et al.[6] Recurrence is also a significant factor for mandibular sarcomas: nearly 50% of the lesions recur at least once. For either site, the recurrences usually appear within the first postoperative year. Distant metastases appear over a period of time after primary treatment but are usually manifest within 2 years.[6] The lungs and brain are most often the sites of secondary deposits.[13]

Prognosis is dependent on several factors. Location of the primary tumor appears important (table 4). Distant metastases reduce ultimate survival to zero.[16] If the sarcoma invades the nasal cavity and sinuses, the likelihood of a favorable prognosis is also greatly reduced, regardless of treatment.[13] Although recurrences allow a potentially dangerous possibility for distant metastases, they are not fatal, and they should be treated aggressively. In cases where osteogenic sarcoma supervenes in Paget's disease, few patients are still living after 5 years. Table 4 presents 5-year survival data from four series.[6,12,15,21]

Table 4. Five-year survivals for patients with osteogenic sarcoma of the jaws located in the mandible and maxilla

Reference	Mandible	Maxilla
Kragh et al[21]	33%	19%
Garrington et al[15]	41%	25%
Finkelstein[12]	50%	30%
Caron et al[6]	24%	33%
Average	37%	26.7%

The low survival of patients with conventional osteogenic sarcoma of the jaws has led to critical evaluation of modes of therapy. Experience with multimodal primary therapy for osteogenic sarcomas of the jaws is limited at present, but even the early apparent successes with such manage-

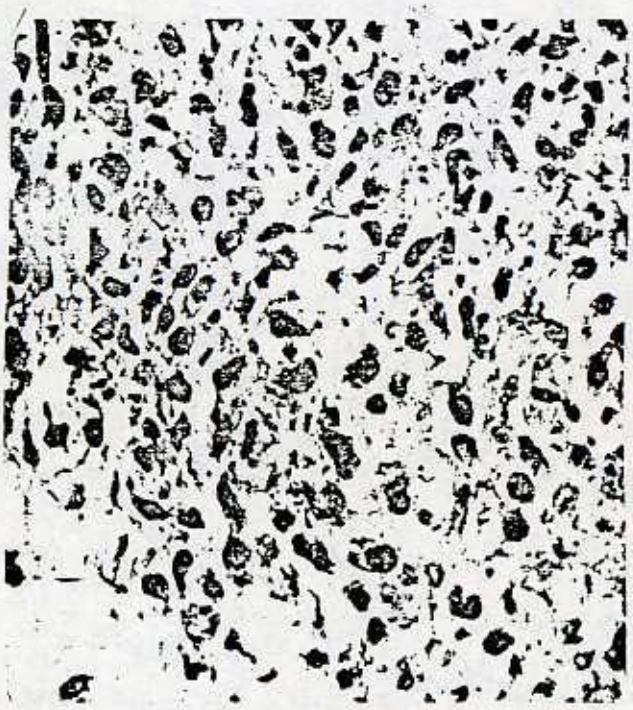

Figure 15. Poorly differentiated focus from an osteogenic sarcoma of the maxilla. Hematoxylin and eosin, ×200.

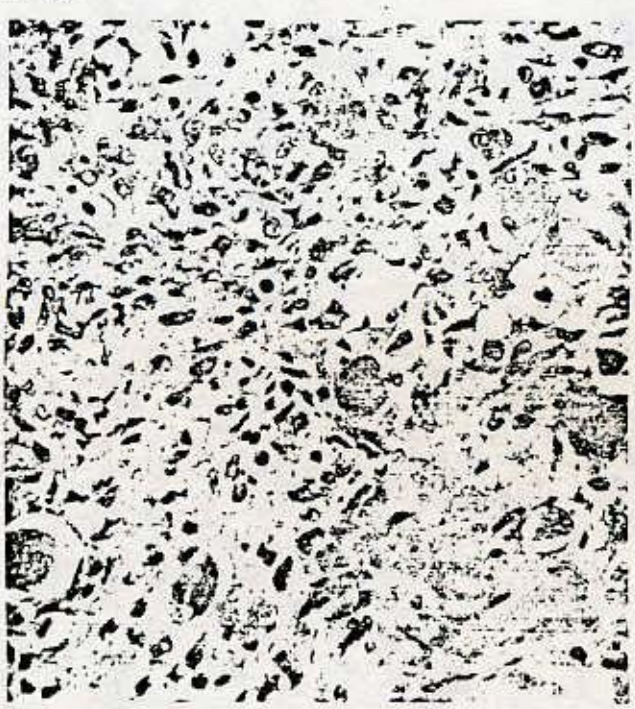

Figure 16. Giant cells dominate this field from an osteogenic sarcoma of the maxilla. Hematoxylin and eosin, ×180.

ment of extrafacial osteogenic sarcomas is currently being re-examined. New randomized trials are being performed to account for findings of late recurrences in patients who received postamputation drugs, decreases in disease-free survival with extended follow-up periods, and rises in long-term survival with surgical treatment alone.

Anatomical Variants of Osteogenic Sarcoma. The classic osteogenic sarcoma is of endosteal origin, although three variants have origins outside the medulla of bone and should be recognized by pathologists and surgeons. Juxtacortical osteogenic sarcomas can be separated into two distinct clinicopathologic entities: parosteal and periosteal. They occur far less frequently in the facial bones than in the long bones; nevertheless, their identification is important because they have a better prognosis than conventional osteogenic sarcomas. The third variant, extraskeletal osteogenic sarcoma, on the other hand, has a prognosis comparable to that of endosteal sarcomas. A rare fourth variant is a well-differentiated lesion and may be misinterpreted as a benign fibrous tumor of the jaws.

Parosteal osteogenic sarcoma. Parosteal osteogenic sarcomas make up less than 4% of all osteogenic sarcomas and less than 1% of all tumors of bone.[32] They are distinguishable from the more common intramedullary osteogenic sarcomas by their gross and microscopic features and by their clinical course.

Parosteal osteogenic sarcomas arise in a juxtacortical position and manifest no appreciable involvement of the medulla at their initial presentation. Radiology demonstrates that the tumor is usually a dense and lobulated mass attached to the cortex by a broad base with the normal cortical configuration interrupted along its base. Peripheral enlargement of the tumor brings with it a peculiar tendency to encircle the involved bone without being attached except at the original base. The density of the tumor, although not uniform, is usually marked, and most of the mass is ossified. New periosteal bone formation is noticeably absent.

The histologic appearance of parosteal osteogenic sarcoma is characteristic, presenting as a rather heavily ossified lesion with proliferating portions that are fibroblastic. Bands of well-formed osteoid and bone are scattered throughout and are most prominent toward the bone of origin. The amount of cartilage present is usually small, and satellite nodules may also be present. The parosteal osteogenic sarcoma is typically well-differentiated (grades 1 and 2), but focal areas may be more histologically active with anaplasia of the fibrosarcomatous areas.

Periosteal osteogenic sarcoma. Periosteal osteogenic sarcomas are distinguishable from parosteal sarcomas by a limitation to the periphery of the cortex of the involved bone, minimal infiltration of the cortex, and radiographic and histologic appearances.[34]

Typically, periosteal osteogenic sarcomas are small lesions found on the surface of the bone. Encirclement of the bone is not found. Microscopically, these lesions manifest lobulated islands of malignant cartilage and spindled stromal areas. Trabeculae of mature osteoid and bone are not found, but the fine lace-like osteoid of osteogenic sarcomas is present in the predominantly chondroid lobules.

Extraskeletal osteogenic sarcoma. Extraskeletal osteogenic sarcoma is seldom encountered in the head and neck. The diagnosis of such a lesion rests on three criteria: (*a*) a uniform morphologic pattern that excludes the possibility of a malignant mixed mesenchymal tumor; (*b*) the production by the sarcomatous tissue of malignant osteoid, bone, or both; and (*c*) the exclusion of an osseous origin.

By 1978 there had been approximately 104 cases of these lesions in the literature.[27] Of these cases, 1.5% occurred in the head and neck. Wide surgical excision is the management of choice. Biologically, these tumors are very malignant and they metastasize frequently. Their behavior is comparable to that of other poorly differentiated soft tissue sarcomas and that of conventional osteogenic sarcoma. The average 5-year survival is only 15.6%.

Well-differentiated intraosseous osteogenic sarcoma. Well-differentiated intraosseous osteogenic sarcoma rarely involves the jaw bones. However, prompt recognition followed by adequate surgery should result in cure in most instances.[34] The tumor usually occupies the medullary portion of the bone only. Most of the tumors are poorly marginated. Expansion of the cortex is usual, and definite destruction of the cortex is seen. However, this destruction is often seen in only small and localized areas.

A fibroblastic proliferation lacking the bizarre character of conventional osteogenic sarcomas and their mitoses typifies the histologic appearance of the stroma. The amount of osteoid within the tumor is variable. Most lesions show irregular, disorganized, fairly heavy seams of osteoid, not unlike that observed in parosteal osteogenic sarcoma. Chondroid areas are rare, as is transformation to more aggressive osteogenic sarcoma.

While possessing metastatic potential, the central, intraosseous, osteogenic sarcoma is predominantly a locally aggressive lesion. The 5-year survival is nearly 100% if the tumor is resectable.[35]

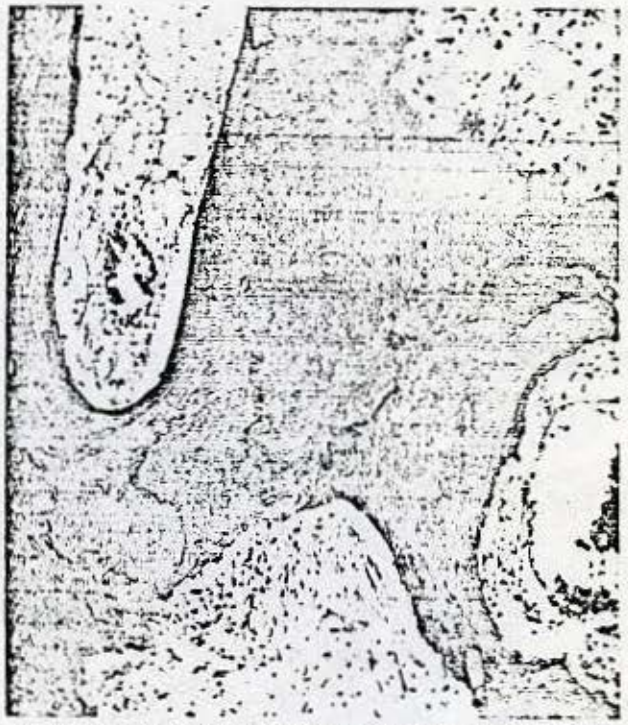

Figure 17. Paget's disease of bone in the mandible. Note the mosaic cement lines and the vascular marrow spaces. Hematoxylin and eosin, ×80.

Paget's Disease of Bone. Histologic distinction between Paget's disease and osteogenic sarcoma does not pose a diagnostic problem for the surgical pathologist. Further, the consequences of the disease in the jaws are not as serious as those of disease in the weight-bearing bones. Its uniqueness lies in the dynamics of the disorder and the potential for malignant degeneration.

Paget's disease of bone is a relatively common focal disorder of bone caused by a localized acceleration of the remodeling of bone. The disease usually appears in middle life. Patients manifesting the disease before the age of 40 usually have a family history of the disease. The spine, pelvis, tibia, femur, and skull are most commonly involved. Clinical disease of the jaw bones is far outnumbered by subclinical involvement. Generally multifocal, the disorder may also manifest different stages of development in different areas of involvement.

The initial change in a focus of Paget's disease is due to osteoclastic proliferation and a resorption of bone. Known as osteoporosis circumscripta, the lesions at this stage often appear as

Figure 18. Sacrococcygeal chordoma presenting with the typical gross lobulated appearance of chordomas (Armed Forces Institute of Pathology #110738)

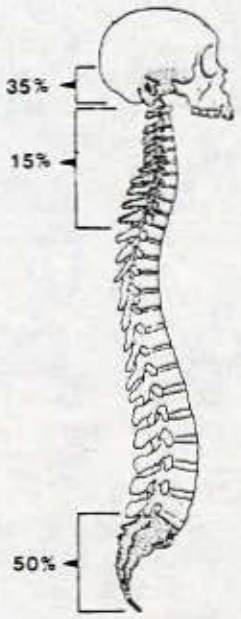

Figure 19. Relative distribution of chordomas.

circumscribed lytic areas and may at times be exuberantly osteolytic. Osteoclasts in this stage have a distinctive appearance: they are large and contain numerous nuclei that may be in excess of 100.

The lesion most often encountered by the biopsy surgeon is a combined osteoblastic and osteoclastic activity in Paget's disease.[31] The acceleration and disorganization of remodeling which occur as a result of this activity produce a disruption of the architectural integrity of the involved bone. Distinctions between cortex and trabeculae are lost. Vascular proliferation is also characteristic of this mixed phase of Paget's disease and it may be striking in its dominance. Osteoblastic activity in this phase results in an increased rate of matrix synthesis and mineralization, but the hyperosteoidosis results from a process wherein the formation of matrix exceeds the deposition of minerals.

The end stage of Paget's disease is the one most familiar to pathologists and also most radiographically characteristic of the disease (fig. 17). An abundance of poorly organized skeletal tissue without evidence of normal remodeling and only little turnover typifies this stage. Osteoblasts and osteoclasts are few in number. The pathognomonic histologic appearance of this phase is the "mosaic" pattern of cement lines, reflecting the rapidity of the remodeling in the preceding stages.[31]

Although malignant degeneration in Paget's disease has a low incidence, it remains a constant threat. Approximately 1% of patients with the disease may develop a superimposed malignancy, and 70% of these patients suffer from the polyostotic form of Paget's disease. The jaws rank low for this complication behind the femur, humerus, and pelvis. The most common malignancy is osteogenic sarcoma.

CHORDOMA

Chordomas are unusual dysontogenetic neoplasms that arise from remnants of the notochord. The distribution of almost 90% of chordomas at the upper and lower extremities of the vertebral column is strong circumstantial evidence that the tumors originate from ectopic chordal nodules rather than from remnants of the notochord persisting in the nucleus pulposus of the intervertebral discs.[3,4,9]

Based on an anatomic predilection, there are three major groups of chordoma: spheno-occipital, vertebral, and sacrococcygeal (fig. 18). More than one third of chordomas occur in the region of the base of the skull, the majority of these arising from the clivus in the region of spheno-occipital synchondrosis (fig. 19). Specifically, sites of origin

Table 5. Patterns of extension of craniocervical chordomas.[4]

Site of origin	Extensions
Dorsum sellae	Intrasellar Intracranial Intraorbit Nasopharyngeal
Clivus	Intracranial Nasopharyngeal
Retropharyngeal vestiges	Towards pharynx
Apical ligament of dens	Intracranial Nasopharyngeal
Nuclei pulposi	Intraspinal Intravertebral Prevertebral

in the craniocervical region are: dorsum sellae, clivus blumenbachii, retropharyngeal notochord vestiges, remnants in the apical ligament of the dens, nuclei pulposi of cervical vertebrae, vestiges in the squama occipitalis, and rare ectopic locations such as the mandible or frontal sinuses. In these sites, chordal remnants may almost always be found in normal adults. However, only a small percentage of these will eventually manifest themselves as true neoplasms.

The clinical picture is determined by the primary location and extension therefrom. Binkhorst et al[4] have described the growth of craniocervical chordomas (table 5). In the cervical vertebral region, there appears to be a special predilection for the second or third cervical vertebrae.

Wright[37] has reported that only a small proportion of craniocervical chordomas have a clinical presentation in the nasopharynx, and the majority of these show evidence of intracranial involvement. The intracranial involvement signifies origin from that site, as is usually the case. The low frequency of nasopharyngeal presentation claimed by Wright, however, was not noted in our study[28] in which more than 90% of the craniocervical chordomas clinically presented with a nasopharyngeal or intranasal mass.[28]

Clinical signs and symptoms are dependent on size and growth extension of the chordoma. In the patients studied by Richter et al,[28] a pattern of neuro-ophthalmologic and otologic symptoms, highlighted by multiple cranial nerve involvement and localized headaches, was characteristic.

Regardless of location, the classic radiologic finding of a chordoma is an expansile osteolytic lesion with a soft tissue mass accompanying the bony lesion.[23] Destructive changes in the clivus and adjacent structures are the dominant plain

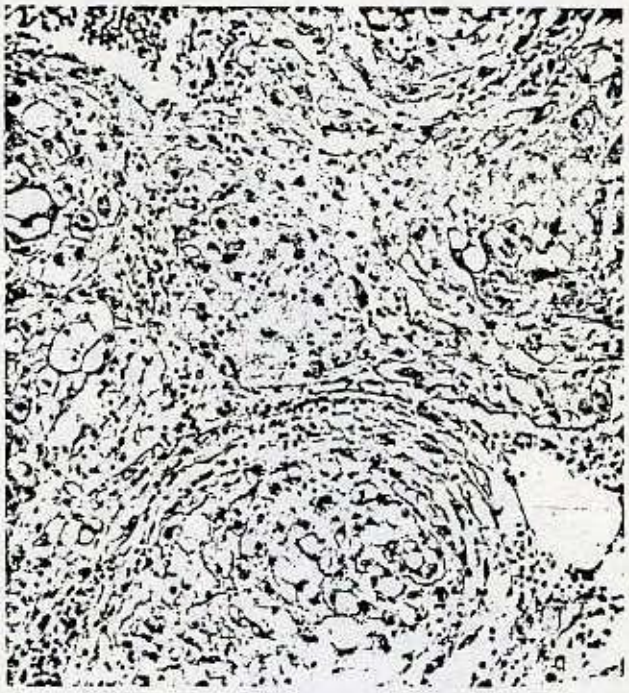

Figure 20. Typical lobulated growth pattern of a chordoma (Armed Forces Institute of Pathology #55-3916). Hematoxylin and eosin. ×40

film findings. According to some authors, the above findings indicate clivus chordoma when accompanied by calcification.[32] Bone erosion or osteolysis of varying degree occurs first in the clivus at the spheno-occipital synchondrosis, from which point it spreads to involve the dorsum sellae, posterior clinoid processes, sellar floor, and sphenoid sinus, and laterally to involve the petrous apices. Less frequently, the destructive process extends anteriorly into the pharynx and inferiorly into the upper cervical segments with involvement of the atlas and axis. Prominent soft tissue masses are often clearly evident in these instances. The destructive changes are typically located in the midline, are more or less symmetrical, and are marked in the clivus. The calcification present in chordomas is either due to dystrophic deposits of calcium within the neoplasm or to sequestration of bone fragments secondary to bone destruction. The calcification is most often nodular or mixed with nodular and cystic components, and is not unlike that seen in craniopharyngiomas, but it is typically retroclival or retrosellar in location.[3,32]

A midline, avascular mass in relation to the clivus is seen on vertebral angiograms. The basilar artery is characteristically displaced superiorly and posteriorly with a prominent posterior convexity. If the chordoma remains confined

Figure 21. Craniocervical chordoma. Abundant intercellular mucoid material separates the chordoma cells. Hematoxylin and eosin, ×150.

Figure 22. Early vacuolar change in cells of a craniocervical chordoma. Hematoxylin and eosin, ×100.

within the clivus or if it extends mainly into the pharynx, few or no abnormalities are evident on air studies.

Light and electron microscopic evaluations reveal that the chordoma is composed of variable numbers and proportions of three different cell types: stellate cells, intermediate cells, and physaliphorous cells.[3,24] The three cells represent different functional stages relative to mucopolysaccharide formation and storage as well as proliferation. Characteristically, the cells are arranged in a lobular growth pattern and exhibit a tendency to grow in cords, in irregular trabeculae, or in a pseudoacinar pattern (fig. 20). There is an abundant intercellular mucoid matrix (fig. 21). Biochemical investigations do not indicate a difference between the acid mucopolysaccharides in the tumor and in the nucleus pulposus, but the storage capacity of individual cells does seem to be enhanced.[24]

Cytophotometric investigations indicate that only the stellate cells are proliferating.[24] The intermediate cells are in the process of vacuolation, and the physaliphorous cells, which are incapable of proliferation, are in the process of self destruction. Vacuolation of cells is a continuous process in the life span of a chordoma cell with destruction of the physaliphorous cell being the terminal event (figs. 22,23, and 24). The stellate

Figure 23. Moderately advanced vacuolation in a different area of the chordoma seen in figure 22. Hematoxylin and eosin, ×80.

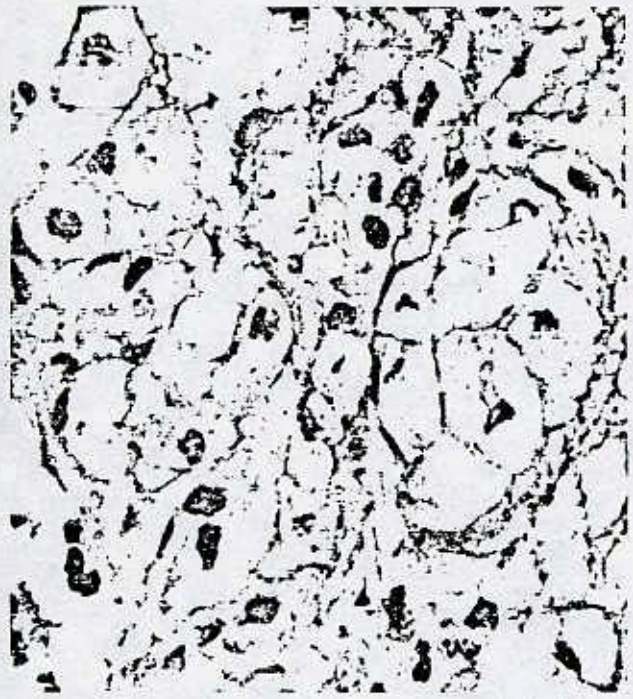

Figure 24. Beginning physaliphorous changes in chordoma cells. Hematoxylin and eosin, ×220.

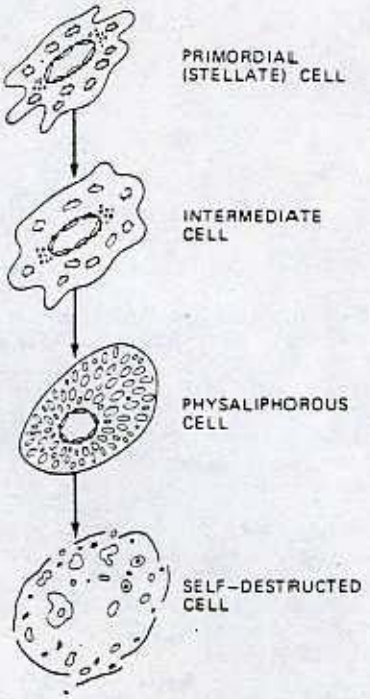

Figure 25. Life cycle of chordoma cells.

cells are poorly differentiated and fibroblast-like, with a prominent nucleus and a very well-developed coarse endoplasmic reticulum. The intermediate cells are characterized by many small and large vesicles, suggesting transformation of stellate cells. The physaliphorous cells are filled with such vesicles in which mucous substances are stored but not produced. Secretion and rupture of such vesicles produce the intercellular matrix.[24] Figure 25 depicts the life cycle of the chordoma cell.

Special mention must be made of a histologic variant of the craniocervical chordoma—the chondroid chordoma.[17,28] This lesion manifests features of chordoma and chondroma or chondrosarcoma in admixture and variable proportions. Recognition of this lesion is important because its prognosis is better than that for nonchondroid chordoma.

The typical (nonchondroid) chordoma of the craniocervical region does not carry a good prognosis. The experience of Dahlin and MacCarty[9] is fairly representative. Only 2 of their 15 patients survived for more than 5 years, with one patient living for more than 18 years after subtotal surgical removal and radiation therapy. Chondroid chordomas, on the other hand, are more favorable to the host: patients with chondroid chordomas in the Mayo Clinic series had an average survival of 15.8 years compared with 4.1 years for typical chordomas.[17]

The malignant potential of a chordoma lies in its origin in critical anatomical sites, a locally aggressive behavior, and an extremely high recurrence rate. Metastases from craniocervical chordomas are rare.[3,32]

Complete surgical removal offers the best chance for cure but is rarely, if ever, achieved in the craniocervical region. Because of the friability and the anatomical location of the tumor, spillage and implantation during operative resection are likely, and these in turn lead to recurrences. Because of the usual slow growth of the neoplasm, prolongation of life, if not cure, may be achieved by combination therapy with postoperative irradiation.[32]

SUMMARY

The major tumors arising from cartilage, bone, and notochordal remnants in the head and neck have been presented with a clinicopathologic correlation for selected lesions: chondrosarcoma, osteogenic sarcoma, and craniocervical chordoma. In the next part of the series on Pathology of Head and Neck Tumors, vasoformative tumors (neoplasms, hamartomas, and reactive lesions) of the blood system will be presented.

RENCES

arlen M, Tollefsen HR, Huvos AG, et al: Chondrosarcoma of the head and neck. *Am J Surg* 120:456–460, 1970.

Ballard R, Weiland LH: Synovial chondromatosis of the temporomandibular joint. *Cancer* 30:791–795, 1972.

3. Batsakis JG, Kittleson AC: Chordomas: otorhinolaryngologic presentation and diagnosis. *Arch Otolaryngol* 79:168–175, 1963.
4. Binkhorst CD, Schierbeck P, Petten GJW: Neoplasms of the notochord. Report of a case of basilar chordoma with nasal and bilateralorbital involvement. *Acta Otolaryngol* 47:10–20, 1957.
5. Bloch DM, Bragoli AJ, Collins DN, et al: Mesenchymal chondrosarcomas of the head and neck. *J Laryngol* 93:405–412, 1979.
6. Caron AS, Hajdu SI, Strong EW: Osteogenic sarcoma of the facial and cranial bones. A review of forty-three cases. *Am J Surg* 122:719–725, 1971.
7. Chaudhry AP, Robinovitch MR, Mitchell DF, et al: Chondrogenic tumors of the jaws. *Am J Surg* 102:403–411, 1961.
8. Coates HL, Pearson BW, Devine KD, et al: Chondrosarcoma of the nasal cavity, paranasal sinuses, and nasopharynx. *Transactions of the American Academy of Ophthalmology and Otology* 84:919–926, 1977.
9. Dahlin DC, MacCarty CS: Chordoma: a study of fifty-nine cases. *Cancer* 5:1170–1178, 1952.
10. Erlandson RA, Huvos AG: Chondrosarcoma: a light and electron microscopic study. *Cancer* 34:1642–1652, 1974.
11. Evans HL, Ayala AG, Romsdahl MM: Prognostic factors in chondrosarcoma of bone. A clinicopathologic analysis with emphasis on histologic grading. *Cancer* 40:818–831, 1977.
12. Finkelstein JB: Osteosarcoma of the jaw bones. *Radiol Clin North Am* 8:425–443, 1970.
13. Fu, Y-S, Perzin KH: Non-epithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx: a clinicopathologic study. II. Fibrous dysplasia, ossifying fibroma, osteoblastoma, giant cell tumor, and osteosarcoma. *Cancer* 33:1289–1305, 1974.
14. Fu Y-S, Perzin KH: Non-epithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx: a clinicopathologic study. III. Cartilaginous tumors (chondroma, chondrosarcoma). *Cancer* 34:453–463, 1974.
15. Garrington GE, Scofield HH, Cornyn J, et al: Osteosarcoma of the jaws. Analysis of 56 cases. *Cancer* 20:377–391, 1967.
16. Goldman RL, Perzik SL: Extraosseous chondrosarcoma of the maxilla. *Arch Surg* 95:301–303, 1967.
17. Heffelfinger MJ, Dahlin DC, MacCarty CS, et al: Chordomas and cartilaginous tumors at the skull base. *Cancer* 32:410–420, 1973.
18. Henderson ED, Dahlin DC: Chondrosarcoma of bone, a study of 288 cases. *J Bone Joint Surg* 45:1450–1458, 1963.
19. Kilby D, Ambegaokar AG: The nasal chondroma: 2 case reports and a survey of the literature. *J Laryngol* 91:415–426, 1977.
20. Kindblom L-G, Angervall L: Histochemical characterization of mucosubstances in bone and soft tissue tumors. *Cancer* 36:985–994, 1975.
21. Kragh LV, Dahlin DC, Erich JB: Osteogenic sarcoma of the jaws and facial bones. *Am J Surg* 96:496–505, 1958.
22. Kragh LV, Dahlin DC, Erich JB: Cartilaginous tumors of the jaws and facial regions. *Am J Surg* 99:852–956, 1960.
23. Lim GHK: Clivus chordoma with unusual bone sclerosis and brainstem invasion. *Australas Radiol* 19:242–250, 1975.
24. Mikuz G, Mydla F, Gütter W: Chordoma: ultrastructural, biochemical and cytophotometric finding. *Beitr Pathol* 161:150–165, 1977.
25. Myers EM, Thawley SE: Maxillary chondrosarcoma. *Arch Otolaryngol* 105:116–118, 1979.
26. Nortje CJ, Farman AG, Grotepass FW, et al: Chondrosarcoma of the mandibular condyle. Report of a case with special reference to radiographic features. *Br J Oral Surg* 14:101–111, 1976.
27. Rao U, Cheng A, Didolkar MS: Extraosseous osteogenic sarcoma. Clinicopathological study of eight cases and review of literature. *Cancer* 41:1488–1496, 1978.
28. Richter HJ, Batsakis JG, Boles R: Chordomas: nasopharyngeal presentation and atypical long survival. *Ann Otol* 84:327–332, 1975.
29. Roca AN, Smith JL Jr, Jing B-S: Osteosarcoma and parosteal osteogenic sarcoma of the maxilla and mandible. *Am J Clin Pathol* 54:625–636, 1970.
30. Sato K, Nukaga H, Horikoshi T: Chondrosarcoma of the jaws & facial skeleton.: a review of the Japanese literature. *J Oral Surg* 35:892–897, 1977.
31. Teitelbaum SL, Bullough PG: The pathophysiology of bone and joint disease. *Am J Pathol* 96:283–354, 1979.
32. Tewfik HH, McGinnis WL, Nordstrom DG, et al: Chordoma. Evaluation of clinical behavior and treatment modalities. *Int J Radiat Oncol* 2:959–962, 1977.
33. Unni KK, Dahlin DC, Beabout JW, et al: Parosteal osteogenic sarcoma. *Cancer* 37:2466–2475, 1976.
34. Unni KK, Dahlin DC, Beabout JW: Periosteal osteogenic sarcoma. *Cancer* 37:2476–2485, 1976.
35. Unni KK, Dahlin DC, McLeod RA, et al: Intraosseous well-differentiated osteosarcoma. *Cancer* 40:1337–1347, 1977.
36. Unni KK, Dahlin DC: Premalignant tumors and conditions of bone. *Am J Surg Pathol* 3:47–60, 1979.
37. Wright D: Nasopharyngeal and cervical chordoma—some aspects of their development and treatment. *J Laryngol* 81:1337–1355, 1967.

Case 13. Mandible: Malignant Fibrous Histiocytomas

Malignant fibrous histiocytoma (MFH) of bone is typically a high-grade sarcoma; rare low- or borderline exceptional cases exist. The preferred sites of origin are the distal and proximal femur, proximal tibia, and proximal humerus and pelvis. About 50% of the tumors have occurred in the region of the knees. There is no age predilection but the neoplasm is seen more often in boys and men.

Approximately 20% of the reported examples have arisen in bones with pre-existing abnormalities. These range from Paget's disease and fibrous dysplasia to bone infarcts. Prior radiotherapy is also implicated.

Radiographically, the lesion is almost always solitary and purely osteolytic. A periosteal reaction is very unusual. Invasion of the adjacent soft tissues is common and confinement to bone, rare.

A literature review of 177 cases indicates that 8 MFH neoplasms arose in the jaws; 5 in the mandible and 3 in the maxilla. Seven of the 177 neoplasms took origin in the skull.

Regardless of site, there is a high recurrence rate (30%)and overall only moderate survivals. The Rizzoli Institute's experience with 90 cases indicates a 34%, 5-year survival, and 28% at 10-years. Hematogenous spread is the dominant form of metastatic spread with the lungs and bones frequently being the sites of initial metastases. Metastasis to lymph nodes is less often but is an ominous sign for prognosis. MFH arising in pre-existing bone abnormalities seems to manifest a poorer prognosis.

In the long bones, surgery alone does not appear to be frequently successful, perhaps due to inapparent distant metastases at the time of initial presentation. Radiation therapy has achieved significant results in some cases.

The minimum necessary histologic criteria are: (1) Identification of 3 cell types: spindled fibroblastic-fibrocytic; cells with a histiocytic morphology and function, and giant-cells (malignant and benign - reactive). Both fibroblastic and histiocytic features are constant with variation from neoplasm to neoplasm. (2) Absence of osteoid. (3) Cartwheel or storiform pattern.

According to degree of cellular pleomorphism, mitoses and type of nuclear chromatin, the tumors can be divided in histologically high or low-grade.

Malignant Fibrous Histiocytoma (MFH) of the Jaws

M. D. Anderson Experience:

Maxilla - 5
Mandible - 6
Age 12-75 (35.4)
Two were post-irradiation sarcomas

All six mandibular patients died (9 mos - 5.7 yrs); local recurrence and distant metastases.
Only one maxillary MFH is free of disease at 27 mos.

Slootweg, P.J.: Fibrosarcoma of the jaws. A study of 7 cases. J. Max-fac. Surg. 12:157-162, 1984.

Taconis, W.K. and Van Rijssel T.G.: Fibrosarcoma of long bones. A study of the significance of areas of malignant fibrous histiocytoma. J. Bone Joint Surg. 67-B:111-116, 1985.

Capanna, R., Bertoni, F., Bacchini, P., Bacci., G, Guerra, A. and Campanacci, M.: Malignant fibrous histiocytoma of bone. The experience at the Rizzoli Institute: Report of 90 cases. Cancer, 54:177-187, 1984.

Case 14. Paraganglioma, jugular

Paragangliomas of the temporal bone arise from paraganglionic tissues on the dome of the jugular bulb, along Jacobsen's nerve (tympanic branch of IX) or Arnold's nerve (post-auricular branch of X). Most originate from the region of the jugular fossa and are known as "glomus jugulare" tumors but extension upwards through the floor of the middle ear means that aural signs and symptoms occur in 98% with conductive hearing loss in 80%.

Less commonly the tumors arise in and remain confined to the middle ear cavity. These paragangliomas arise from paraganglionic tissue along the course of Jacobson's nerve as it crosses the promontory of the basal turn of the cochlea.

Their histologic appearance is not unlike other paragangliomas with chief cells and supporting cells both participating in the neoplastic process. Curability of jugular tumors is low and the hazard of intracranial extension always present.

All paragangliomas of the head and neck display a diffuse and intense immunostaining for neuron-specific enolase and in addition can manifest a variety of cellular hormone products; most frequently serotonin and leu-enkephalin. The hormone substances rarely elicit a clinically apparent endocrine or metabolic imbalance.

Perhaps more interesting than the diagnosis is the differential diagnosis of lesions that may simulate paragangliomas involving the middle ear.

The earliest symptoms of a glomus jugulare tumor are pulsatile tinnitus and hearing loss. Later on, there may be bleeding from the ear and cranial nerve VII, IX, X, and XI palsy. The characteristic finding in the early stage is a red or deep pink mass in the middle ear. The paraganglioma may occupy the mesotympanum, the hypotympanum, or fill the entire middle ear cavity. When the drum is perforated, the tumor can present as a vascular polyp.

A bruit may be heard over the ear. Usually there is a conductive hearing loss and a sensorineural loss may result from labyrinthine involvement. Plain x-rays and tomograms show a middle ear mass with or without destruction of bone.

Among the non-paraganglionic tumors capable of producing some or many of these characteristic features are:

1. Vascular lesions –
   (a) high jugular bulb
   (b) uncovered or aberrant intratympanic carotid artery
   (c) arterio-venous malformations
   (d) aberrant branches or aneurysm of internal carotid artery.
   (e) persistent stapedial artery
2. Inflammatory –
   (a) cholesterol granuloma
   (b) aural polyp
3. Choristoma (salivary)

4. Neoplastic lesions –

(a) meningioma

(b) adenomatous tumor of the middle ear

(c) hemangioma

(d) metastatic and primary carcinomas

High jugular bulb: The jugular bulb normally lies below the floor of the hypotympanum. In 3-6% of temporal bones, it has been found to be placed above this level and in the middle ear. The anomaly is usually unilateral. The high jugular bulb may be in contact with the tympanic membrane or be more medially placed. There may be a thin bony cover or the bulb may lie exposed. Usually the tympanic membrane is intact but if the bulb projects superiorly enough there may be a conductive deafness because of interference with the incus and stapes.

By otoscopic exam the high jugular bulb usually is in the posterior portion of the lower middle ear while the paraganglionic tumors lie more towards the middle of the mesotympanum. The bulb also lacks the red-purple colon of a paraganglioma; it has a bluish color.

Ectopic intratympanic internal carotid artery: This anomaly is extremely rare. The ectopic carotid enters the ear posteriorly, passes through the entire length of the middle ear and regains a normal position in the petrous apex. The lesion is usually unilateral. Warning signs, if present, include; pusatile tinnitus, fullness and hearing loss and occasionally vertigo.

In the normal situation, the artery lies in front of the cochlea and the tympanic cavity. It is separated from the tympanum by a thin bony plate. The anomalous artery lies lateral to the "vestibular line" – a line which extends vertically down from the vestibule and represents the most medial extent of the middle ear in the majority of temporal bones.

Meningiomas: These lesions can present in the middle ear either as an extension from an intracranial meningioma or be primary in the middle ear. By 1983, approximately 20 cases of primary middle ear meningiomas have been reported in the English and French literature.

"Hemangiomas": I have never seen a hemangioma of the middle ear and that diagnosis should be very reserved. Anteriovenous malformation may involve the region but so-called hemangiomas are really pyogenic granulation tissue related to inflammatory diseases in the middle ear. In like manner hemangiomas of the tympanic membrane are extremely rare and do not involve the middle ear.

Valvassori, G.E., and Buckingham, R.A.: Middle ear masses mimicking glomus tumors: radiographic and otoscopic recognition. Ann. Otol. 83:606-612, 1974.

Anderson, J.M., Steven, J.C., Sundt, T.M., Stockard, J.J., and Pearson, B.W.: Ectopic internal carotid artery seen initially as middle ear tumor. JAMA, 249:2228-2230, 1983.

Balkany, T.J., Meyers, A.D., and Wong, M.L.: Capillary hemangioma of the tympanic membrane. Arch. Otolaryngol. 104:296-297, 1978.

Dayal, V.S., Lafond, G., van Nostrand, A.W.P., and Holgate, R-C.: Lesions simulating glomus tumors of the middle ear. J. Otolaryngol. 12:175-179, 1983.

Lawson, W.: Glomus bodies and tumors. N.Y.J. Med. 80:1567-1575, 1980.

Lack, E.E., Cubilla, A.L., and Woodruff, J.M.: Paragangliomas of the head and neck region. A pathologic study of tumors from 71 patients. Hum. Pathol. 10:191-218, 1979.

Reddy, E.K., Mansfield, C.M., and Hartman, G.V.: Chemodectoma of glomus jugulare. Cancer 52:337-340, 1983.

Jenkins, H.A., and Fisch, U.: Glomus tumors of the temporal region. Arch. Otolaryngol. 107:209-214, 1981.

Ogura, J.H., Spector, G.J., and Gado, M.: Glomus jugulare and vagale. Ann. Otol. 87:622-629, 1978.

Case 15. Neuroendocrine carcinoma (adult neuroblastoma, nasal) cavity

This lesion is a nasal neuroblastoma, belonging to a class of lesions that may be subdivided into two broad groups; neuroblastoma and neuroendocrine carcinoma. Silva et al have divided the lesions into: (a) neuroblastoma without olfactory differentiation, (b) neuroblastoma with olfactory differentiation and (c) neuroendocrine carcinoma.

Neuroblastoma without Olfactory Differentiation

1. Small cells with bland nuclei and inconspicuous nucleoli
2. Fibrillary material between the cells
3. Sheets or poorly demarcated groups of cells separated by fine CT trabeculae
4. Variable mitoses and rare Homer-Wright rosettes
5. Grimelius, variable

Neuroblastoma with Olfactory Differentiation

1. Olfactory rosettes are hallmark.

Neuroendocrine Carcinoma

1. Well demarcated groups of cells with slender CT trabeculae
2. Variable size of cells with little architectural pattern

3. No fibrillary component
4. More cytoplasm than neuroblastoma groups
5. More often positive Grimelius
6. Admixture of glands with intimate relation to tumor cells

For general recognition of nasal neuroblastomas, the following other features are helpful: (1) compartmentalized "lobules" of cells, (2) thin fibrovascular septa, (3) overall vascularized background matrix, commonly with hemorrhage, (4) foci of dystrophic calcification, (5) perivascular pseudorosettes, (6) occasional cases contain a melanin-like pigment.

The location of these lesions is fairly restricted to the high nasal cavity. A primary maxillary origin is always suspect and likely not possible except only "apparent" by extension.

There is no apparent sex predilection. The tumor is uncommon under 10 years of age and is rare in infancy. The age distribution usually shows a bimodal distribution with a peak in the 11-20 years group and a steady rise to a second peak in the 51-60 years group.

Focal extension is the primary mode of morbidity. Lymph node metastases occur in about 15% of patients and 8% are said to have distant metastases at time of diagnosis.

Histologic grading and staging of the neoplasm can be of prognostic significance. Unpublished data from the AFIP indicate four histologic grades, primarily based on nuclear characteristics. Briefly, Grade I has very uniform nuclei and essentially no mitoses. Grade II has some anisonucleosis and occasional mitoses. Both

I and II usually have readily identifiable neurofibrillary matrix and often show pseudorosettes. Grade III tumors exhibit true rosettes ("neuroepithelioma") and nuclear anaplasia. Grade IV tumors are likened to poorly differentiated or anaplastic carcinomas.

A proposed staging follows:

Disease confined to nasal cavity

Disease confined to nasal cavity and one or more sinuses

Disease extending beyond the above; includes invasion of orbit, base of skull, intracranium, cervical nodes, or distant sites.

Elkon D, Hightower SI, Meng LL, et al.: Esthesioneuroblastoma. Cancer 44:1087-1094, 1979.

Bailey B, Barton S.: Olfactory neuroblastoma. Arch. Otolaryngol. 101:1-5, 1975.

Baker D, Perzin K, Conley J.: Olfactory neuroblastoma. Otolaryngol. Head and Neck Surg. 87:279-283, 1979.

Naessen, R.: The identification and topographical localization of the olfactory epithelium of man and other mammals. Acta Otolaryngol. 70:51, 1970.

Naessen R.· An inquiry on the morphological characteristics and possible changes with age in the olfactory region of man. Acta. Otolaryngol. 71:49, 1971.

Silva EG, Butler JJ, Mackay B, et al.: Neuroblastomas and neuroendocrine carcinomas of the nasal cavity. Cancer 50:2388, 1982.

Elkon D.: Olfactory esthesioneuroblastoma, in Nasal Tumors in Animals and Man. Vol. II, 129-147, Eds. G. Reznik, S.F. Stinson, CRC Press, Boca Raton, Florida, 1983.

Case 16. Squamous cell carcinoma with small cell component

This peculiarly differentiating oral carcinoma has areas of variably differentiated squamous cell carcinoma. A small-cell component that although appears to be separate, does have origin from the surface and from transition points in the squamous cell carcinoma. It is not, in my opinion, a collision tumor even though the small cell component does have features of a poorly differentiated salivary carcinoma with tubular, abortive gland-like spaces. There are some features of an ameloblastoma but I believe these are spurious and I do not know of such an aggressive peripheral ameloblastoma. Because of the variable differentiation with squamous carcinoma admixed with a small cell carcinoma, the possibility of an intraoral Merkel's carcinoma is raised. Recall that approximately 25% of cutaneous Merkel carcinomas have an associated, recognizable squamous cell carcinoma. Proof of this possibility requires identification of the neuroendocrine nature of the small cells. This was not done. Neurone-specific enolase, if positive, would assist in confirmation, but a negative immunoreactivity is not definitive. Grimelius reactions should be taken in a similar context. Electron-optic finding of neurosecretory granules would be nearly proof-positive.

Failing the above, the neoplasm represents a variable differentiation of a squamous cell carcinoma. In the upper aerodigestive tract, this is most often seen in the pharynx and larynx. The tumors as might be appreciated are high-grade carcinomas.

Gould, V.E., Moll, R., Moll, I., Lee, I, and Franke, W.W.: Neuroendocrine (Merkel) cells of the skin: hyperplasias, dysplasias, and neuorplasms. Lab. Invest. 52:334-353, 1985.

Winkelmann, R.K.: The histochemistry of the Merkel cell neuroepithelial endings in cat and rabbit skin and oral mucosa. Acta Dermatovener. 62:383-387, 1982.

Silva, E.G., Mackay, B., Goepfert, H., Burgess, M.A., and Fields, R.S.: Endocrine carcinoma of the skin (Merkel-cell carcinoma). Pathol Annu. 19(Suppl. II) 1, 1984.

Edmondson, H.D., Browne, R.M., and Potts, A.J.C.: Intraoral basal cell carcinoma. Brit. J. Oral Surg. 20: 239, 1982.

Case 17. Nasal cavity, papillary squamous cell carcinoma

This malignancy is a papillary squamous carcinoma. The entire lesion is malignant and it is more than intra-epithelial (focal areas of invasion). Architecturally there is a resemblence to a Schneiderian papilloma but note the carcinoma is exophytic and not inverting. It is possible that in the development of the carcinoma it passed through a clinically unrecognized Schneiderian papilloma phase; there is no histologic evidence to support this, however.

It is my opinion the papillary carcinomas of the oral cavity, larynx and sinonasal tract are related to human papilloma-virus (HPV) infection with a second initiating event producing the malignant transformation. HPV has been found in Schniederian papillomas, oral papillomas, laryngeal papillomas and verrucous carcinomas at the same sites.

Localized papillary carcinomas can be controlled by conservative surgery, more extensive ones like the seminar case require more aggressive management, i.e., surgery and irradiation.

Whether or not related to a Schneiderian papilloma, the latter lesions on the lateral wall of the nasal-sinus tract have a significant incidence of malignancy; in many instances, arising from the papilloma. These carcinomas are variable in their epidermoid differentiation and are invasive.

The accompanying reprints summarizes Schneiderian papillomas. Key points are:

(1) Whether septal or lateral wall, the recurrence rates are nearly equal; approximately 40%.

(2) Malignancy in a septal papilloma is an oddity. I have seen only one and know of one other. Lateral wall papillomas, on the other hand have a significant association; approximately 15%.

(3) Because of spreading or multifocal origin, adjacent sinuses must always be explored in apparently nasal Schneiderian papillomas.

(4) Even without malignant transformation, the Schneiderian papilloma can be locally destructive and may require extensive surgery.

(5) Cylindrical cell papillomas are histologic variants and have the same rate of recurrence. They may be confused by the unwary as adenocarcinomas.

PATHOLOGY CONSULTATION

NASAL (SCHNEIDERIAN) PAPILLOMAS

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The mucosa of the nasal cavity and paranasal sinuses differs from the remainder of the airway system in that it is embryologically derived from *ectoderm*. This uniqueness carries over into the morphogenesis of a controversial group of lesions: *papillomas* of the nasal cavity and sinuses. Controversy surrounding papillomas can be divided into problems relating to: a) nomenclature, b) histopathology, c) biologic behavior, and d) malignant potential.

Nomenclature. Perhaps no group of lesions has acquired so many names since their description.[1] Even papillomas may be inaccurate since the neoplastic nature of the lesions has not been proven. The often-used term, "transitional," carries an unwarranted implication that a histologically specific and identifiable epithelium gives rise to the papilloma. It is an ambiguous term and should be abandoned.[2]

Since the mucosa is embryologically unique, some recognition of this characteristic should be carried in the designation of its tumors. A term carrying that recognition has been used in the past and, while eponymic, clearly identifies the mucosa and lesions derived from it. Schneiderian mucosa and Schneiderian papillomas are suggested as the most suitable alternatives to the numerous synonyms being used.[3] This name honors one of the early investigators, J. V. Schneider, and cannot be confused with any other anatomically located papilloma (Fig. 1).[3]

Histopathology. Schneiderian papillomas arise from a proliferation of reserve or replacement cells of the mucosa. In its fullest expression, this proliferation assumes two basic architectural patterns: inverting, and fungiform or exophytic. Mixtures may also occur.

These two basic forms further segregate by rather specific localization in the upper airway. Fungiform papillomas are nearly restricted to the nasal septum or its environs. Lateral wall and/or sinuses are typical sites of the inverted papilloma (Fig. 2A). Why such a distribution exists is unknown but there are significant implications for biologic activity and the surgeon is cautioned to always provide localization to the pathologist for an accurate assessment of clinical course. Septal papillomas tend to remain localized to the septum and association with carcinoma is very rare. In contrast, lateral wall papillomas are often not restricted to the site, often show sinus involvement or are localized in a sinus, and have a significant association with carcinoma.

The predominant cell type in either the lateral wall or septal papilloma is epidermoid. Vestiges of the overlying epithelium may be found with variable frequency. On occasion, an entire papilloma may be composed of modified columnar epithelium. If so constituted the diagnostic term, cylindrical cell papilloma, has been used.[1]

Biologic Behavior and Malignancy. The major clinical and therapeutic problem with any form of Schneiderian papilloma is recurrence. Recurrences may be multiple and delayed. The rate of recurrence, in major series, has ranged from 28% to 67%.[2] Lateral wall lesions manifest a higher recurrence rate than those of the septum. Extension and/or metaplastic involvement occurs with lateral papillomas (Fig. 2B) but has not been documented from septal papillomas.

Left untreated, papillomas can be locally invasive, especially the lateral lesions. Erosion of bone, and death by local extension is possible.

Ascribing a premalignant quality to Schneiderian papillomas is unwarranted but a patient with a lateral wall papilloma is clearly at risk for the develop-

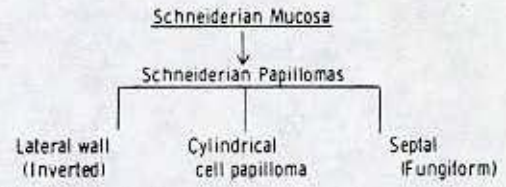

Fig. 1. Schneiderian papillomas arise from ectodermally derived mucosa and yield three histomorphologic varieties. The pure cylindrical cell papilloma is unusual and is predominantly a lateral wall or sinus lesion.

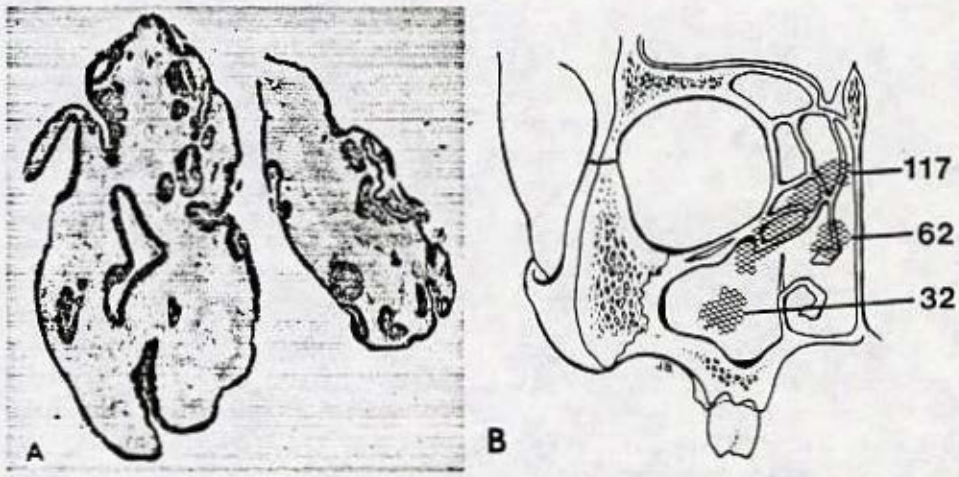

Fig. 2. A) Typical low-power light microscopic appearance of a lateral wall, inverting Schneiderian papilloma. The lack of an inflammatory reaction is typical (H & E, x10). B) Anatomic location of 211 Schneiderian nasal papillomas as derived from the literature. Note the preponderance of papillomas involving both the lateral nasal wall and adjacent sinus.

ment of associated carcinoma. Associated is to be stressed since histologic documentation of the transformation of a papilloma to carcinoma is limited. This event likely represents less than 2% of the reported cases. The usual circumstance is that of squamous cell carcinoma arising in the same anatomic region but without evidence of origin from papilloma. This event is more common and approximates a frequency of 20%.[4]

Treatment is surgical removal with a margin of normal tissue. Lateral wall lesions require inspection of adjacent sinuses. Too-conservative excision is tantamount to recurrent disease. Radiotherapy has no role in the primary management of a Schneiderian papilloma.

SUMMARY

Schneiderian papillomas are unique lesions of the nasal cavity and paranasal sinuses. Most often epidermoid in histologic appearance, the Schneiderian papilloma favors two sites: the septum and lateral wall of the nasal cavity. In both sites recurrences are frequent. Papillomas of the lateral wall, in addition, have a significant association with carcinoma.

REFERENCES

1. Hyams VJ. Papillomas of the nasal cavity and paranasal sinuses: a clinicopathological study of 315 cases. Ann Otol Rhinol Laryngol 1971; 80:192-206.

2. Batsakis JG. Tumors of the head and neck: clinical and pathological considerations. 2nd ed. Baltimore: Williams & Wilkins, 1979:131.

3. Ridolfi RL, Lieberman PH, Erlandson RA, Moore OS. Schneiderian papillomas: a clinicopathologic study of 30 cases. Am J Surg Pathol 1977; 1:43-53.

4. Yamaguchi KT, Shapshay SM, Incze JS, Vaughn CW, Strong S. Inverted papilloma and squamous cell carcinoma. J Otolaryngol 1979; 8:171-8.

THE PATHOLOGY OF HEAD AND NECK TUMORS: NASAL CAVITY AND PARANASAL SINUSES, PART 5

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Abstract: Nasal polyps and epithelial papillomas of the sinonasal tract often manifest similar clinical signs and symptoms. The similarity ends, however, when one considers their disparate biologic behavior. Polyps are associated with atopy, infection, and some metabolic, systemic disorders, whereas papillomas are enigmatic in pathogenesis and do not have an association with possible precursor disorders. While recurrences of nasal polyps may be an annoyance for the patient, such recurrences lack the local aggressiveness of the papilloma. Malignancies are rare in nasal polyps, whereas the frequency of malignancies in papillomas is both statistically and biologically significant. In this report, selected aspects of nasal polyps are considered and serve to contrast with the clinicopathologic evaluation of epithelial papillomas.

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Although they are histogenetically dissimilar, nonglandular papillomas and polypoid lesions of the nasal cavity and paranasal sinuses manifest similar clinical signs. The pathogenesis of both types of lesion remains unknown, and individual cases of these lesions are biologically and pathologically unique. In this study, the fifth section in the series on the pathology of tumors of the head and neck, I present selected aspects of nasal polyps and a clinicopathologic review of papillomas of the nose and paranasal sinuses.

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NASAL POLYPS

The pathogenesis of the common nasal polyp continues to elude scientists. Allergy, atopy, infection, and vasomotor impairment have been proposed as factors in the development of this lesion.[2,3,12,14,21,33] Because of the marked stromal edema associated with polyps, it is tempting to regard the production of polyps as a result of the disorder of the vascular bed and impairment of homeostasis. Ultrastructural studies of polyps have revealed venules with consistently open endothelial junctions, a finding suggesting that vascular leakage has taken place and that vascular injury is at least a secondary factor in the evolution of the nasal polyp.[2,33]

Classification of nasal polyps according to a predominant cellular infiltrate is not reliable.[33] Eosinophils, regarded by some as indicative of an allergic state, are not reliable markers. Eosinophilia varies from patient to patient regardless of the atopic state, and the degree of eosinophilia may be dependent only on recent contact with an allergen. Except for tenuous light microscopic findings (described below), routine light microscopic and electron microscopic examinations of the conventional nasal polyp have not been helpful in elucidating the pathogenesis of the polyp.[2,3,14,15,22,33]

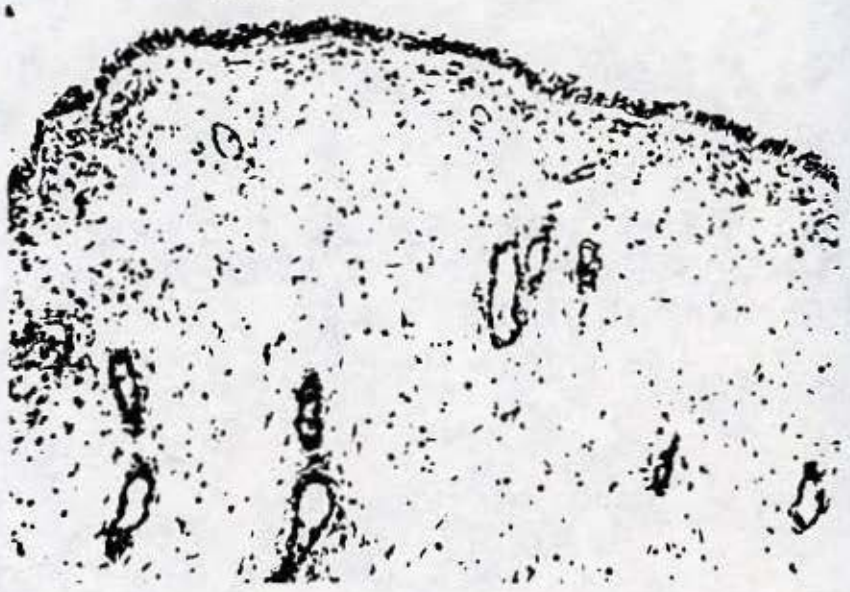


Figure 1. Nasal polyp manifesting homogenization of basement membrane and only scattered inflammatory cells. This appearance is nonspecific. Hematoxylin and eosin, ×84.5.

Nasal polyps are most common in the upper part of the lateral nasal wall around the middle turbinate, especially in the middle meatus and in the ethmoidal region. They also arise under the superior and middle turbinates, at the hiatus semilunaris and the infundibulum. Reasons for this predilection include the comparative delicateness of the mucosal stroma in these regions and the closely approximated ridges, which exaggerate any interference with vascular and lymphatic supply initiated by edema of the mucosa.

Polyps may be solitary and unilateral or multiple and bilateral. Usually soft and gelatinous, they are movable, do not bleed easily, and are insensitive to manipulations. Increase in the size of a polyp is accomplished almost exclusively by an accumulation of intercellular fluid. The surface epithelium is usually of the respiratory type (fig. 1) with any metaplastic changes dependent on pressure or friction from surrounding bony walls, trauma, infection, and exposure to air currents.

The mucous glands in nasal polyps are markedly reduced in density, with the majority being found in the distal half of the polyp.[28] As a consequence of their density reduction, the mucus production of polyps is very slight as compared with normal nasal mucous membrane.[15] The glands of the polyp are almost exclusively tubular, manifesting themselves in various types but considerably different in appearance from the glands of the nasal mucosa. The glands in polyps probably originate in the downgrowth of epithelium, secondary canalization, and dichotomous division of tubules.[28] Degeneration of the glands leads to cyst formation and loss of secretory epithelium. The cysts themselves play no role in the formation of the polyp.

The usually unexciting light microscopic appearance of the stroma of nasal polyps contains the key to the mechanisms of origin. The stroma is composed of an edematous connective tissue framework that contains stellate mesenchymal cells, mucous glands, telangiectatic blood vessels, and inflammatory cells. In the electron microscopic studies, the stromal changes are manifested by massive edema, presumably brought about by the liberation of vasoactive chemicals from mast cells.[2] Collagen synthesis is also active in the stroma of the polyp. This synthesis is regarded as an attempt of stromal cells to check the expansion of volume caused by the excess of intercellular fluid.[2]

The nasal polyp is prone to nearly all secondary changes possible in polypoid lesions: infarct, fibrosis, neovascularization, and surface epithelial changes.[1]

NASAL POLYPS AND ASTHMA

The nature of the association between nasal polyps and bronchial asthma remains obscure; it is unknown whether nasal polyps arise in response to stimuli resulting from the same pathologic mechanisms that are active in asthma, or just occur coincidentally with bronchial asthma. Further, the true incidence of nasal polyps concomitant with asthma is not known. The reported prevalence of asthma in patients with nasal

Figure 2. Nasal polyp from a patient with cystic fibrosis. While there is cystic dilation, inspissation of secretions, and goblet-cell hyperplasia, this histologic appearance is nonspecific with respect to etiologic basis. Hematoxylin and eosin. ×69

polyps has ranged from 2.9% to 72%,[12] and the prevalence of nasal polyps in patients with asthma has varied from 23% to 42%.[12]

The association of the two disorders, however, appears to be more frequent than can be accounted for by chance. Nasal polyps are common in patients with asthma who are nonatopic and are most common in those asthmatics who develop a sensitivity to salicylates.

The histopathology of the nasal polyps is not sufficiently distinctive to allow definitive classification. Similarly, the nasal polyps in atopic and nonatopic patients are not significantly different.

NASAL POLYPS AND CYSTIC FIBROSIS

The upper respiratory tract is often abnormal in patients with cystic fibrosis. They have symptoms of nasal obstruction more frequently than do normal children, and nasal polyps, otherwise rare in children, are not infrequently found in patients with cystic fibrosis (6%–20%).[22,27] Nasal polyposis, with or without associated wheezing, may also be the major, and at times the presenting, clinical feature in older individuals with cystic fibrosis. In the younger patient, nasal polyps may precede clinical diagnosis of the disorder by several years.[27]

There have been only a few reports attempting to provide histologic information as a basis for etiologic differentiation of polyps and, in short, there are no conclusive histologic findings that characterize nasosinal cystic fibrosis. The presence of large, mucous retention cysts with inspissated secretions and a hyperplasia of mucous glands is suggestive of but not restricted to cystic fibrosis (fig. 2). The stroma of the polyp from a patient with cystic fibrosis is similar to that from an atopic individual, although there may be a greater degree of inflammation in the former. Squamous metaplasia is common to all forms of nasal polyps.

Oppenheimer and Rosenstein[19] have reviewed the foregoing nonspecific findings and point to three histologic differences that may indicate that the tissue changes are associated with cystic fibrosis. Two of these are negative findings. Changes considered nearly pathognomonic of atopy are: marked hyaline thickening of the basement membrane of the surface epithelium, a significant stromal infiltration of eosinophils, and a predominantly neutral mucin in exudates. The hyalinization of the basement membrane is an exaggeration of the process seen in the tracheobronchial tree of asthmatics. Polyps from patients with cystic fibrosis manifest a delicate, barely visible basement membrane without submucosal hyalinization.

Severe tissue eosinophilia may be the rule in the atopic polyp (eosinophil counts of 70%–90%), but it is the exception in cystic fibrosis.

Alcian blue-periodic acid-Schiff stains demonstrate a preponderance of acid mucin in the glands and cysts of polyps and in the surface mucous blanket of patients with cystic fibrosis. The atopic polyp manifests a preponderance of neutral mucins.[19]

ANTROCHOANAL POLYPS

The antrochoanal polyp (nasoantral, benign nasopharyngeal, postnasal, and recurring polyp) is a benign, usually solitary polypoid lesion that arises from the paranasal sinuses, especially the lateral wall of the maxillary sinus. The polyp grows by extension from the antrum through its ostium into the middle meatus and then into the posterior choana; it may extend into the nasopharynx.

Compared to the inflammatory or "allergic" polyp, the antrochoanal polyp is infrequent. Heck et al[8] found that 56 (3.25%) of 1,720 patients with nasal polyps had an antrochoanal polyp. Sirola[23] reported a frequency of 6.2% of nasal polyps in his Helsinki series. Data from various series indicate that about 71% of patients with antrochoanal polyps are between 10 and 39 years of age.[7,8,23,29]

Figure 3. Atypical stromal fibroblasts in an antrochoanal polyp. Hematoxylin and eosin. ×120.6

There was a slight predominance of males and there was no significant allergic history among these patients.

Only rarely has the location of origin been a sinus other than the antrum, but there have been reports of sphenochoanal polyps, and some have been thought to arise from the ethmoid air cells.

The diagnosis of an antrochoanal polyp is strongly suggested when an opacified maxillary antrum is expanded and there is a nasopharyngeal mass. Radiography of the sinuses yields negative findings only rarely. In the series of Heck et al,[5] a unilateral sinus lesion on the involved side was found in 57% of the cases, and 42% showed bilateral involvement of the maxillary or other sinuses. Evidence of slight but definite expansion of the involved maxillary antrum was noted in all of the patients reported by Towbin et al.[29] Erosion of the antral wall may occur if the polyp fails to pass posteriorly.

As indicated above, the antrum is the prime site of origin. Here the polyp may arise from any wall, usually the lateral wall, and gains entrance to the nasal fossa by way of an ostium, usually a large accessory ostium.

Gross examination reveals the typical antrochoanal polyp to be a large, solitary, grayish white, and smooth polyp with a stalk of variable length. It may be seen on posterior rhinoscopy either projecting from a choana or completely filling the nasopharynx. With increased growth, it may drop below the level of the soft palate into the oropharynx. The pedicle or stalk, if found, will in most instances pass from the polyp anteriorly into the middle meatus. There are, as a rule, no other polypoid changes or polyps in the nose. The smooth and glistening, grayish white surface can serve to differentiate this polyp from the pebbled, mulberry-like hyperplastic, polypoid reaction of the posterior turbinal tips.

Histologic examination shows that the antrochoanal polyp does not usually differ substantially from the nasal polyp except when there are secondary alterations. Two of these alterations, while not unique to the antrochoanal polyp, may lead to erroneous diagnosis. In general, there is a paucity of mucous glands in the antrochoanal polyp, and this is thought to reflect the antral mucosal origin of the polyp. However, this paucity combined with stromal-cell atypia in the solitary polyp may lead the pathologist to a misdiagnosis of stromal malignancy. In the present author's experience, such stromal atypia has occurred most often in the antrochoanal polyp. Compagno et al[4] presented the clinical, microscopic, and gross pathologic features of 14 cases of intranasal and paranasal sinus polyposis with unusual stromal-cell atypia. The stromal atypia, described as pseudosarcomatous by Smith et al,[24] is characterized by the presence, in nasal polyps, of large, bizarre, pleomorphic spindle cells with often prominent, hyperchromatic nuclei (figs. 3 and 4). No other feature except for erosion signaled any differences from a conventional polyp. This observation suggests that caution should be exercised in the diagnosis of stromal malignancy. While the cells may present a cytologically alarming appearance, no recognizable pattern of malignancy

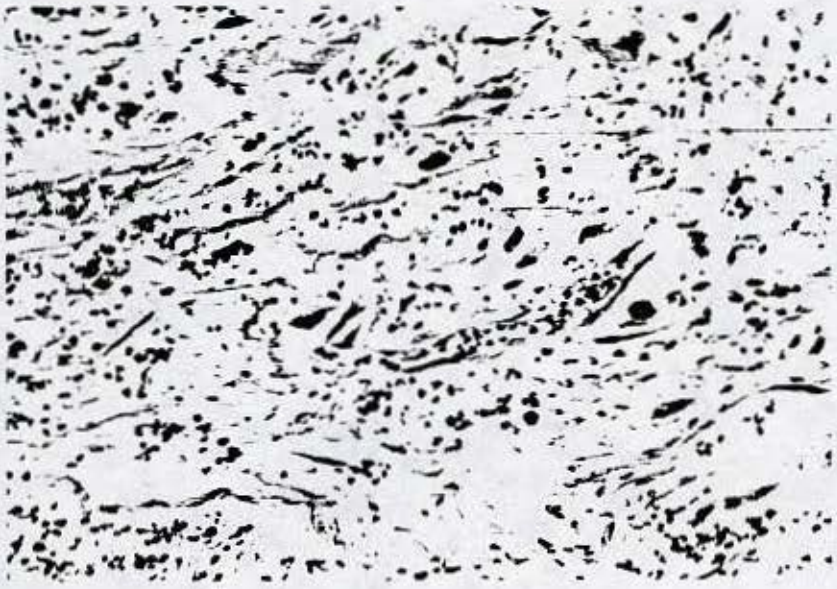


Figure 4. Hyperchromatic and bizarre-shaped stromal cells in an antrochoanal polyp. Except for these modified cells, the polyps contain no other features of a malignant tumor. Hematoxylin and eosin, ×117.

is present, and a clear distinction from sarcoma is usually possible on histopathologic grounds alone. The present consideration is that the atypical stromal cells are tissue histiocytes and facultative histiocytes.

The second alteration relates to the vulnerability of the antrochoanal polyp to vascular compromise. Infarct, necrosis, and organization by vascular granulation tissue and vessels may present a clinical and histopathologic picture simulating that of a juvenile angiofibroma.

The antrochoanal polyp is best treated by the Caldwell-Luc operation. Simple snare or avulsion polypectomy is followed by a 20% recurrence rate.

SCHNEIDERIAN PAPILLOMAS

The mucosa that lines the nasal cavity and paranasal sinuses, although indistinguishable by light microscopy from endodermal or foregut-derived respiratory epithelium, is unique in embryogenesis in that it is of ectodermal origin.[20] It is derived from the nasal placodes that invaginate to form the primitive nasal sacs and then ultimately the nasal and paranasal cavities. Historically, this ectoderm has been associated with Victor Conrad Schneider, and over the years has acquired the eponym of Schneiderian mucosa.[20]

The controversial papillomas of the nasal cavity and paranasal sinuses arise from the Schneiderian mucosa, and since they are unique in histology, biologic course, and location, the term *Schneiderian papilloma* seems appropriate. The diagnostic use of the term includes the designations given to the papillomas based on their location (i.e., lateral wall), septal or histopathologic architecture (i.e., fungiform or sessile), and inverted or cylindrical cell structure.[9] Not included is the vestibular papilloma, which is an epidermal lesion lacking any of the histologic or biologic features of the Schneiderian papilloma.

Often behaving as neoplasms, the Schneiderian papillomas probably arise from a proliferation of reserve or replacement cells located at the basement membrane of the mucosa.[13] This proliferation, whose stimulus is unknown, thickens the epithelium and assumes an inverting, fungiform, or combination growth pattern. The biologic tendency of such growths is to form a metaplastic epithelium that is transitional only in that it tends toward squamous-cell differentiation. Depending on the degree of metaplasia, variable amounts of respiratory or cylindrical cells are present in any Schneiderian papilloma. On rare occasions, the papilloma is composed almost entirely of cylindrical cells—hence the histologic subtype, cylindrical-cell papilloma.[9]

Although the use of Schneiderian papilloma as a diagnostic term should be encouraged, there is merit and necessity in accurate clinical anatomic localization of the papillomas. To that end, the term should be qualified by the descriptions *lateral wall* or *septal*. This terminology is justified by differences in biologic behavior with different locations. Septal papillomas tend to remain on the septum (with occasional involvement of the roof and floor of the nasal cavity). Reflecting

Figure 5. Schneiderian papilloma of the septal type or so-called fungiform papilloma. Hematoxylin and eosin, ×69.

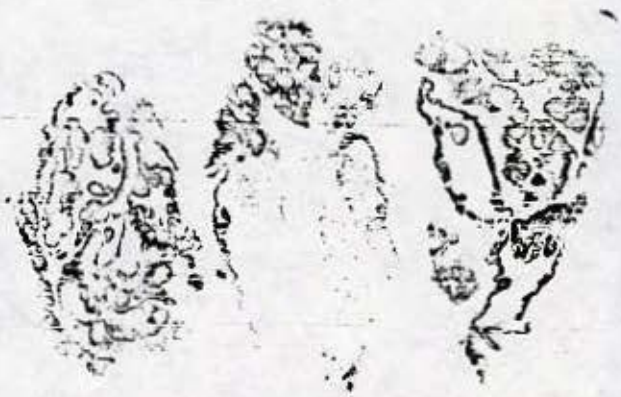


Figure 6. Sections of a Schneiderian papilloma of the lateral-wall type or so-called inverted papilloma. Hematoxylin and eosin, ×10.4.

perhaps the relative immunity of the septum to malignancy, an association between carcinoma and the Schneiderian septal papilloma is a medical curiosity. In contrast, papillomas of the lateral wall may involve multiple sites—sinuses, floor and roof of the nasal cavity, and nasolacrimal duct—and their association with squamous-cell carcinoma is well documented.[5,6,10,11,16-18,20,25,30-32] In some patients the lateral papilloma may be confined to the paranasal sinuses, but in most cases, the sinuses are involved by a direct extension.[26]

Schneiderian papillomas are not common lesions; they occur with from 1/50 to 1/25 of the frequency of nasal polyps, and they represent from 0.4% to 4.7% of surgically removed nasal tumors.[25,31]

The etiology of Schneiderian papillomas is unknown except that there is no relationship to allergy or to nasal polyps. Men are involved more often than women, and although the age range of patients extends from the second to the seventh decade of life, the mean age at clinical presentation is nearly 50.[18]

The symptoms of Schneiderian papillomas vary, but features differing from those of nasal polyps, choanal polyps, and other benign nasal tumors are not readily evident. Nasal obstruction is the most common complaint, and the fact that a considerable number of patients have had previous nasal surgery is significant.[9,11,26]

The gross appearance of the papillomas depends on location and extent. In general, they are bulkier and firmer than nasal polyps and lack the translucency of the polyp.

Radiographic findings with Schneiderian papillomas also depend on the size and extent of the lesions. A unilateral thickening or opacification of the antrum, often with similar changes in the ethmoids, are the most common observations. The frontal and sphenoid sinuses are only rarely involved. Extension into the nasopharynx may be present. There may be evidence of bone erosion, which is usually manifested in the medial wall of the maxillary antrum.[31] It should be underscored that this bone involvement is due to pressure and not to direct invasion of bone. If invasion is present, it is inconsistent with a diagnosis of papilloma and indicates either misdiagnosis or an associated carcinoma.

Schneiderian papillomas grow in two architectural patterns; (*a*) papillary and exophytic, and (*b*) inverted, with an inwardly invaginating epithelial growth into underlying stroma. An admixture of both patterns may occur. The papillary form tends to favor a septal location and has been called fungiform by Hyams.[9] The inverted type is most often found on the lateral wall of the nasal chamber and in the sinuses.

The papillary or fungiform papilloma is the form most consistent with the pathologist's concept of papilloma wherein the epithelial proliferation is supported by a thin central core of connective tissue (fig. 5). Inversion of the epithelial masses is usually not present.[9] The predominant epithelial growth of the inverted form of papilloma is directed into the underlying stroma instead of as a surface proliferation (fig. 6).

The predominant cell type in both forms is epidermoid with individual cells having a prominent cellular border. Intercellular bridges can be easily demonstrated, especially in the cell layers

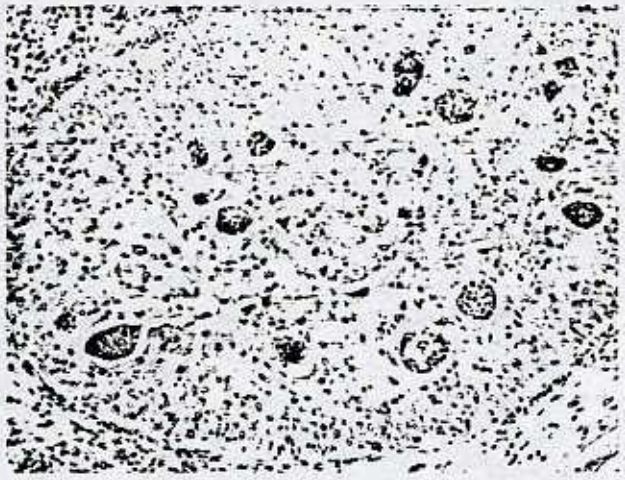


Figure 7. Inverting Schneiderian papilloma manifesting mucous cysts, some of which contain cellular debris. Hematoxylin and eosin, ×75.9.

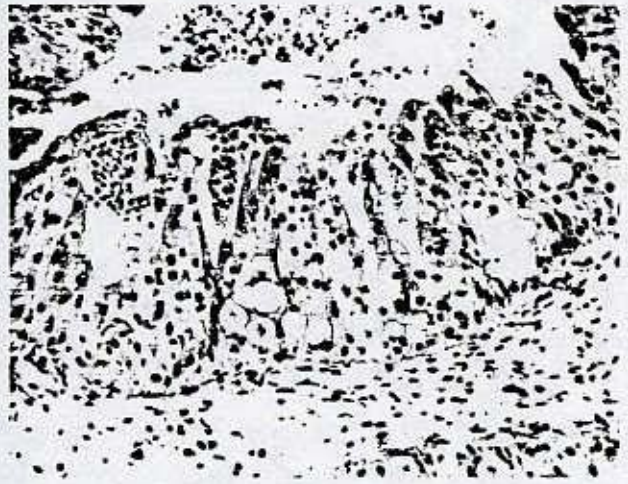


Figure 9. Microscopic field from an inverting papilloma composed entirely of eosinophilic cylindrical cells. Hematoxylin and eosin, ×86.25.

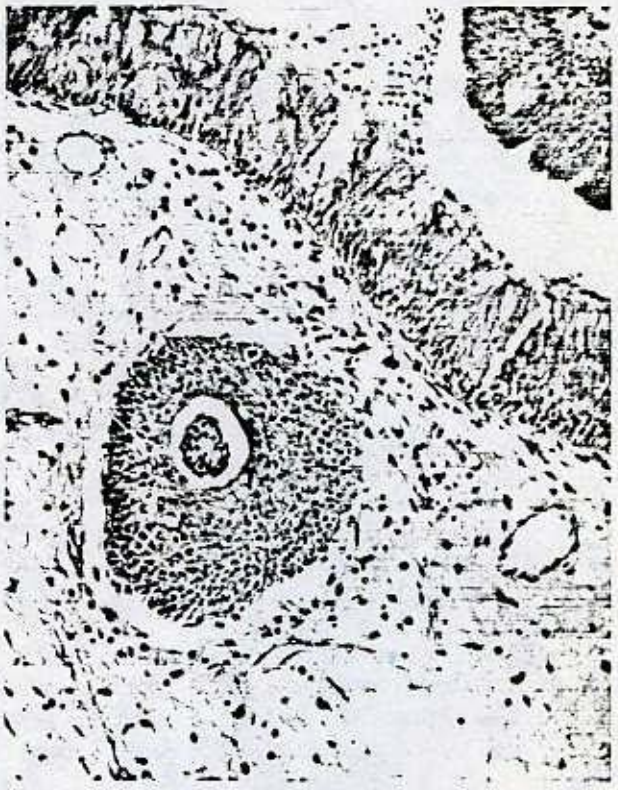


Figure 8. Hyperplastic respiratory epithelium overlying a tangentially cut focus of inverting papilloma. Hematoxylin and eosin, ×88.

adjacent to the usually distinct basement membrane. Microscopic mucous cysts can be identified in both forms. These cysts very likely represent entrapped mucous cells of normal respiratory mucosa (fig. 7).[9]

Individual cell keratinization is minimal, and surface keratin is most often not abundant. In this regard, extensive keratinization in Schneiderian papillomas is atypical and should alert the pathologist to other diagnoses. The stroma of the inverted papilloma may be myxomatous and similar to the nasal polyp, or it may be compact and fibrous. Unless there has been secondary ulceration, the inflammatory component of the papillary and inverted papillomas is minimal. In addition to the epidermoid cell population characterizing the papillomas, a surface layer of typical ciliated, columnar epithelium may be found in various microscopic fields, strengthening our contention that the histogenesis of these lesions is based on basal-cell replacement (fig. 8).

On occasion, a Schneiderian papilloma will be comprised of proliferating, multilayered columnar cells—so-called cylindrical cells (figs. 9 and 10). These modified respiratory epithelial cells possess an eosinophilic (almost oncocytic) cytoplasm and a uniform nucleus. Cilia may be present. Hyams[9] has designated these papillomas as cylindrical-cell papillomas. They usually exhibit both inverting and exophytic components. While their biologic behavior does not differ from the other histologic forms of Schneiderian papillomas, their recognition is important. Hyams[9] relates that if the cylindrical-cell papilloma possesses numerous intramucosal cysts, it is frequently misdiagnosed as rhinosporidiosis. My consultation service has found, however, that the misdiagnosis most often submitted is papillary adenocarcinoma.

Over the course of time, the Schneiderian papillomas have been considered as: (*a*) uniformly

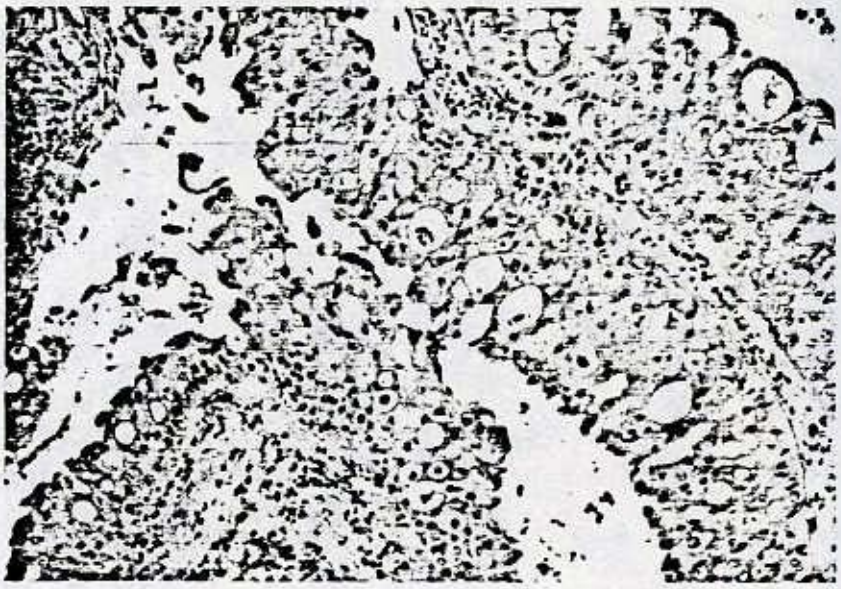


Figure 10. So-called cylindrical cell papillomas. This lesion is a form of Schneiderian papilloma and may be confused with adenocarcinoma. Hematoxylin and eosin, ×97.5.

malignant, (*b*) premalignant, and (*c*) perfectly benign. None of these appraisals are appropriate for these histologically benign, yet locally aggressive, lesions.

The major clinical and therapeutic problem relates to recurrences. These may be due to persistence or extension of the metaplastic process and are also determined by the adequacy of surgical removal. Table 1 presents the recurrence rate as described in eight reports.[5,9,10,16–18,20,25] Recurrences may be multiple and may also be delayed for years. Papillomas on the lateral nasal wall and within paranasal sinuses manifest a somewhat higher recurrence rate than those presenting on the nasal septum. A prediction of those papillomas that will recur cannot be made by histopathologic examination, despite some reports to the contrary.[26]

The literature concerning malignancy in association with Schneiderian papillomas is controversial. Fechner and Alford,[6] for example, could only accept a documented occurrence of carcinoma in 3 of 300 cases of papilloma they reviewed. It is also quite clear that there is no histologic change in a papilloma that heralds the advent of carcinoma. However, as table 2 indicates, the association of squamous-cell carcinoma with Schneiderian papillomas is real, especially for the lateral-wall or inverted type. Association does not imply evolution, and although the percentage frequency may be alarming, the number of such examples is small. Combined lesions of papilloma and carcinoma (squamous-cell) may be segregated into three categories: (*a*) carcinomas and papillomas occupying the same anatomical region but with no evidence that the papilloma has given rise to the cancer; (*b*) papillomas with a focus of in situ or invasive carcinoma within them; and (*c*) papillomas that do not recur after treatment but are succeeded by invasive carcinoma. The first and third categories clearly represent carcinomas in association with papillomas, and the majority

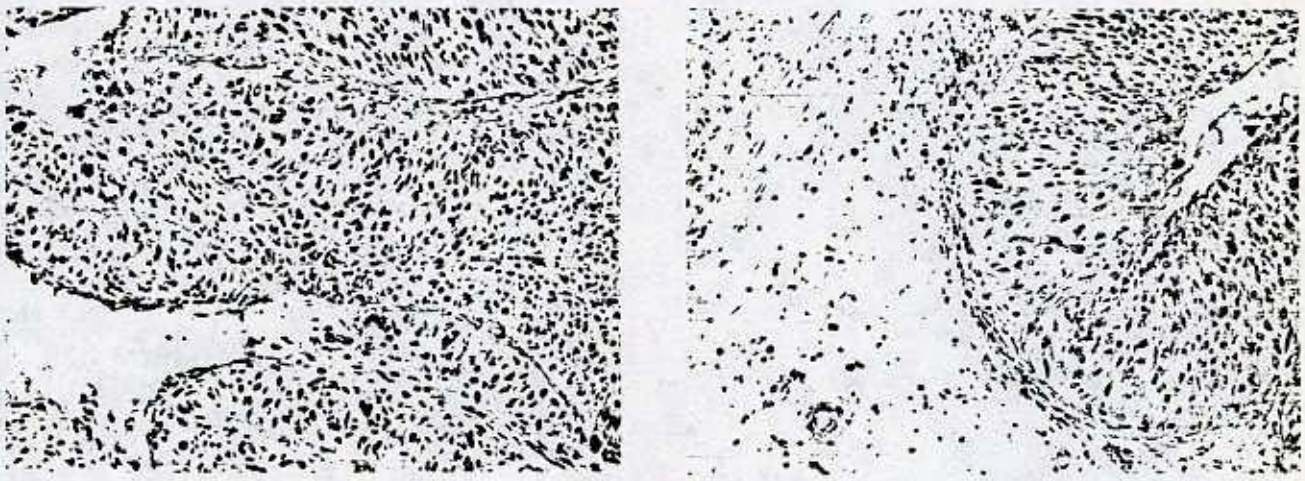
Table 1. Recurrence rate of nasal papillomas.

Reference	No. of patients with recurrence/no. studied (%)
Norris[16,17]	16/57 (28)
Lampertico et al[10]	9/19 (47)
Cummings and Goodman[5]	18/29 (62)
Oberman[18]	9/21 (42)
Hyams[9]	45/79 (57)
Snyder and Perzin[25]	17/35 (49)
Ridolphi et al[20]	20/30 (67)

Table 2. Association between Schneiderian papillomas and squamous-cell carcinoma.[a]

Reference	No. with papillomas	No. with carcinomas	% frequency of associations
Lasser et al[11]	17	4	24
Yamaguchi et al[32]	15	8	53
Hyams[9]	149	19	13
Snyder and Perzin[25]	39	8	21
Suh et al[26]	57	4	7
Trible and Lekagul[30]	30	3	10
Ridolfi et al[20]	30	1	3

[a] *Data relate exclusively to the inverted form of papilloma.*



A B

Figure 11. Surface (A) and depth (B) of a squamous-cell carcinoma of the paranasal sinus. Although the growth pattern may simulate an inverting Schneiderian papilloma, these lesions are entirely malignant and usually have no relationship to a preexisting papilloma. Hematoxylin and eosin, ×65.55.

of so-called examples of malignant transformation of a papilloma are of this type. Histologic documentation of transformation is required for the second group and the percentage of such cases is relatively low—very likely less than 2% of reported cases.

Radiation therapy is to be condemned as a primary treatment for Schneiderian papillomas. The tumors are not recognized for their radiosensitivity, and the probable induction of carcinoma has been cited in earlier reports.[6,11,25]

Surgical removal is the treatment of choice, but there is a lack of uniformity in the type and extent of the surgery required.[21] Needless to say, management should be tailored to the individual case so as to ensure total removal of the proliferating epithelium. Removal by loops, snares, or simple excision nearly ensures recurrence. If the lateral wall of the nasal cavity is involved, there is a high probability of sinus involvement, and thus the paranasal sinuses should be inspected carefully. If there is extensive involvement of either the lateral nasal wall or the paranasal sinuses, the papillomas should be removed by a lateral rhinotomy or maxillectomy, using a Weber-Fergusson incision.[9,25,31]

If there is no objective evidence of the infiltrating factors for papillomas, ascribing a premalignant quality to the lesions is unwarranted. The increased risk of malignancy in relation to such a modified epithelium is, however, undeniable. The pathologist is cautioned that even when a carcinoma manifests an inverting pattern, the neoplasm has not necessarily arisen in a papilloma (figs. 11 A and B).

SUMMARY

The nasal cavity and paranasal sinuses are the sites of origin of nearly every histopathologic type of neoplasia. These range from the most common form, the squamous-cell carcinoma, to mucous-gland tumors and supporting-tissue malignancies. This report has presented a brief histopathologic overview of the non-neoplastic and commonplace nasal polyp and two of its variants, the antrochoanal polyp and the nasal polyp of the patient with cystic fibrosis. In addition, a summary of the clinicopathologic aspects of the Schneiderian papillomas has been offered. These biologically peculiar tumors, with their high recurrence rate and association with carcinomas, lie between the polyp and the recognizable malignancy of the nasal cavity and sinuses. Squamous-cell and mucous-gland neoplasms will be the focus of the next part of this series.

REFERENCES

1. Busuttil A: Dysplastic epithelial changes in nasal polyps. *Ann Otol Rhinol Laryngol* 87:416–420, 1978
2. Busuttil A, More IAR, McSeveney D: Ultrastructure of the stroma of nasal polyps. Cilia in stromal fibroblasts. *Arch Otolaryngol* 102:589–595, 1976.
3. Cauna N, Hinderer KH, Manzetti GW, et al: Fine structure of nasal polyps. *Ann Otol Rhinol Laryngol* 81:41–58, 1972.
4. Compagno J, Hyams VJ, Lepore ML: Nasal polyposis with stromal atypia. Review and follow-up study of 14 cases. *Arch Pathol Lab Med* 100:224–226, 1976.
5. Cummings CW, Goodman ML: Inverted papillomas of the nose and paranasal sinuses. *Arch Otolaryngol* 92:445–449, 1970.
6. Fechner RE, Alford DD: Inverted papilloma and squamous cell carcinoma. *Arch Otolaryngol* 88:507–512, 1968.
7. Hardy G: The choanal polyp. *Ann Otol Rhinol Laryngol* 66:306–323, 1957.
8. Heck WE, Hallberg OE, Williams HL: Antrochoanal polyps. *Arch Otolaryngol* 52:538–548, 1950.
9. Hyams VJ: Papillomas of the nasal cavity and paranasal sinuses: a clinicopathological study of 315 cases. *Ann Otol Rhinol Laryngol* 80:192–206, 1971.
10. Lampertico P, Russell WO, MacComb WS: Squamous papilloma of upper respiratory epithelium. *Arch Pathol* 75:293–302, 1963.
11. Lasser A, Rothfeld PR, Shapiro RS: Epithelial papilloma and squamous cell carcinoma of the nasal cavity and paranasal sinuses. *Cancer* 38:2503–2510, 1976.
12. Moloney JR, Collins J: Nasal polyps and bronchial asthma. *J Dis Chest* 71:1–5, 1977.
13. Muller R, Bechtelsheimer H, Tolsdorff P: Zur formalen Genese des sog. invertierten Papillom (invertiertes Epithelium). *Zeitschrift für Laryngologie, Rhinologie, Otologie und ihre Grenzgebiete* 52:300–308, 1973.
14. Mygind N: Immunohistopathology of allergic rhinitis and conditions allied. *Clin Otolaryngol* 3:325–342, 1978.
15. Nakashima T, Hamashima Y: Loss of secretory activity in the glands of nasal polyps. *Ann Otol Rhinol Laryngol* 88:210–216, 1979.
16. Norris HJ: Papillary lesions of the nasal cavity and paranasal sinuses. I. Exophytic squamous papillomas. A study of 28 cases. *Laryngoscope* 72:1784–1797, 1962.
17. Norris HJ: Papillary lesions of the nasal cavity and paranasal sinuses. II. Inverting papilloma. A study of 29 cases. *Laryngoscope* 73:1–17, 1963.
18. Oberman HA: Papillomas of the nose and paranasal sinuses. *Am J Clin Pathol* 42:245–258, 1964.
19. Oppenheimer EH, Rosenstein BJ: Differential pathology of nasal polyps in cystic fibrosis and atopy. *Lab Invest* 40:445–449, 1979.
20. Ridolfi RL, Lieberman PH, Erlandson RA, et al: Schneiderian papillomas: a clinicopathologic study of 30 cases. *Am J Surg Pathol* 1:43–53, 1977.
21. Samter M: Nasal polyps. An inquiry into the mechanism of formation. *Arch Otolaryngol* 73:334–341, 1961.
22. Shwachman H, Kulczycki LL, Mueller HL, et al: Nasal polyposis in patients with cystic fibrosis. *Pediatrics* 30:389–401, 1962.
23. Sirola R: Choanal polyps. *Acta Otolaryngol* 61:42–48, 1965.
24. Smith CJ, Echevarria R, McLelland CA: Pseudosarcomatous changes in antrochoanal polyps. *Arch Otolaryngol* 99:228–230, 1974.
25. Snyder RH, Perzin KH: Papillomatosis of nasal cavity and paranasal sinuses (inverted papilloma, squamous papilloma). A clinicopathologic study. *Cancer* 30:668–690, 1972.
26. Suh KW, Facer GW, Devine KD, et al: Inverting papilloma of the nose and paranasal sinuses. *Laryngoscope* 87:35–46, 1977.
27. Taylor B, Evans JNG, Hope GA: Upper respiratory tract in cystic fibrosis. Ear-nose-throat survey in 50 children. *Arch Dis Child* 49:133–136, 1974.
28. Tos M, Mogensen C: Mucous glands in nasal polyps. *Arch Otolaryngol* 103:407–413, 1977.
29. Towbin R, Dunbar JS, Bove K: Antrochoanal polyps. *Am J Roentgenol* 132:27–31, 1979.
30. Trible WM, Lekagul S: Inverting papilloma of the nose and paranasal sinuses: report of 30 cases. *Laryngoscope* 81:663–668, 1971.
31. Vrabec DP: Inverted Schneiderian papilloma. A clinical and pathological study. *Laryngoscope* 85:186–220, 1975.
32. Yamaguchi KT, Shapshay SM, Incze JS, et al: Inverted papilloma and squamous cell carcinoma. *J Otolaryngol* 8:171–178, 1979.
33. Whiteside TL, Rabin BS, Zetterberg J, et al: The presence of IgE on the surface of lymphocytes in nasal polyps. *J Allergy Clin Immunol* 55:186–194, 1975.

Case 18. Fibrosarcoma, low-grade, ethmoid sinus

Fibrosarcomas of the sinonasal tract are unusual neoplasms and while they have a "better" prognosis than other sarcomas of this region, including fibrosarcomas of bone, they are difficult to control thereby yielding recurrences over a prolonged period.

Fu and Perzin concluded that fibrous lesions, benign and malignant are uncommon in the paranasal sinus – nasal cavity. Of 23 fibrous tissue tumors from these sites, they had 4 fibromas, 6 examples of fibromatoses and 13 fibrosarcomas. The tumors occur over a wide age range (childhood to late adulthood) and manifest a significant male preponderance. The antrum and the nasal cavity are sites of predilection.

Large bloc resection appears to be the best method to avoid recurrences. Death is rarely from metastases, but from local invasion.

In this seminar case, the fibrosarcomatous proliferation is accompanied by an increased convolution, tortuosity and hyperplasia of mucosal ducts. This has produced an apparent inversion that led to the misdiagnosis of inverted papilloma.

The typical clinical presentation is that of a polypoid mass (2-8 cm.) with a deceptive circumscription. Adjacent bone can be destroyed either by direct invasion or by expansion atrophy. Infiltrative margins are usually blunt.

Marked pleomorphism is not a feature. Mitoses are always found, but are rarely numerous. Histologic grading should always be done since grade has some bearing to recurrences and survival.

Enterline, H.T.: Histopatholgy of sarcomas. Semin. Oncol. 8:133-155, 1981.

Swain, R.E., Sessions, and Ogura, J.H.: Fibrosarcoma of the head and neck: A clinical analysis of fourty cases. Ann. Otol. 83:439-444, 1974.

Fu, Y-S, and Perzin, K.H.: Non-epithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx. A clinicopathologic study . VI. Fibrous tissue tumors (fibroma, fibromatosis, fibrosarcoma). Cancer 37: 2912-2928, 1976.

Batsakis, J.G., Rice, D.H., and Howard, D.R.: The pathology of head and neck tumors: Spindle cell lesions (sarcomatoid carcinomas, nodular fasciitis, and fibrosarcoma) of the aerodigestive tracts. Head and Neck Surg. 4:499-513, 1982.

Case 19. Sinonasal cavity: extramedullary plasmacytoma

The lesional tissue is a pure culture of plasma and plasmacytoid cells which manifested a monoclonality for light-chains, i.e., a plasmacytoma. The accompanying reprint by Batsakis and its references summarize current knowledge on these lesions.

Perhaps the most important histologic differential diagnosis is primary sinonasal melanomas for these lesions where the plasma cell features are less prominent.

PATHOLOGY CONSULTATION
PLASMA CELL TUMORS OF THE HEAD AND NECK

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In order of frequency, the plasma cell lesions affecting the head and neck are multiple myeloma, extramedullary plasmacytoma, plasma cell granuloma, and solitary plasmacytoma of bone. All except plasma cell granuloma are neoplastic and they are interrelated. The solitary plasmacytoma of bone is regarded as a form of multiple myeloma. The extramedullary plasmacytoma may be a lesion of local significance only or may terminate in a disseminated disease, myelomatosis, that differs clinically and prognostically from multiple myeloma.

A localized plasma cell lesion in the head and neck poses considerable diagnostic and therapeutic problems for the head and neck surgeon. While there is a rather abundant literature on these tumors, the authors have either perpetuated the opinions of others or have indiscriminately lumped the several categories of disease into one.

Confronted with a plasma cell tumor, the head and neck surgeon has several, yet a limited number of, diagnostic options: 1) a localized manifestation (bone or soft-tissue) of existing systemic disease, *multiple myeloma*; 2) an *extramedullary plasmacytoma* without evidence of systemic disease; 3) a localized, intraosseous lesion, *solitary plasmacytoma of bone;* or 4) a benign inflammatory lesion having no relationship to the preceding three disorders, the *plasma cell granuloma*. Each of these lesions will be discussed, but the integral cell, the plasma cell, requires definition.

Plasma cells are now widely accepted as the secretory form of B-lymphocytes, differing principally by the presence of abundant protein-synthesizing equipment in the cytoplasm. Plasma cell diseases are a group of clinical disorders characterized by growth of a single clone of cells that elaborates a single, homogeneous immunoglobulin molecule. The most important and numerous of these diseases is multiple myeloma. It may be regarded as a malignant plasma cell disorder arising from a single transformed cell of the B-cell series of lymphocytes.

Neoplastic proliferation of this single line of plasma cells produces a specific protein, as if under constant antigenic stimulation. Because a specific globulin is produced that is unique for each patient, the plasma cell diseases are also referred to as monoclonal gammopathies. The monclonal protein is comprised of one heavy-chain class (IgG, IgA, IgM, IgD, or IgE) and one light-chain class (κ or λ), and is often referred to as an M (myeloma protein).

Diagnosis of plasma cell dyscrasias is based on the combination of clinical, radiologic and clinical laboratory evaluations. In the latter, the presence and classification of the paraproteinemia is most important and definitive. Production and detection of the paraproteinemia is, however, not uniform. Nonsecretory forms exist and detection is clearly based on tumor mass or tumor burden, a factor very important in localized plasmacytomas.

PLASMA CELL GRANULOMA

Plasma cell granuloma is the least controversial of the plasma cell tumors. It has a predilection for the oral cavity. Because of the numbers of plasma cells normally present in the upper aerodigestive tracts, their presence in reactive and inflammatory lesions is expected. In instances where they are unusually abundant in such reactions, the designation *plasma cell granuloma* is applied as a diagnostic term. In the oral cavity, plasma cell granuloma is a lesion primarily of the periodontal tissues. The gingiva is the area most frequently involved, with maxillary and mandibular gingivae equally affected. The tumors are seen on the marginal, interdental and attached gingiva; alveolar mucosa is spared.

Bone loss may or may not be present. There is no sex predilection and the lesions can occur at any age. Multiple plasma cell granulomas are rare. Recurrences are dependent on the underlying cause of the reactive lesions.

Microscopically, plasma cell granulomas can be distinguished from plasmacytoma. The stromal matrix is vascular and reactive. The plasma cells, while numerous, do not exist in pure or nearly pure "culture" and are accompanied by other inflammatory cells. The plasma cells show no cytologic abnormalities and are usually concentrated in areas surrounded by connective tissue septae. Russell bodies may be present.

SOLITARY PLASMACYTOMA OF BONE

Solitary plasmacytoma of bone is now recognized as a rather unusual presentation of multiple myeloma.[1,2] For this reason and because its presentation in facial bones is uncommon, it is the second least controversial of the plasma cell disorders. Patients with solitary plasmacytoma of bone are defined as having a radiographically solitary lytic lesion and no evidence of plasmacytosis in a random bone marrow examination. Detection of a paraprotein or M-band in serum or urine does not exclude the diagnosis.[1,2] There is no absolute proof that any such lesion is indeed "solitary." The spine, pelvis, and femur are the sites of predilection. There is a male preponderance and the average age of onset is about one decade less than that for multiple myeloma.[1,2]

The radiographic appearance is usually a multicystic area of rarefaction. Compared with the sharply demarcated, destructive lesions of multiple myeloma, the solitary plasmacytoma is characterized as being larger, trabeculated, and multilocular.

The presence of protein abnormalities is obviously important for follow-up. If a paraprotein is present, it should disappear after primary treatment. Persistence or reappearance indicates residual tumor or dissemination.

Dissemination is nearly always an event that occurs in the first 3 to 5 years after primary diagnosis.[2] Nearly 50% of the patients exhibit this spread of disease which is almost exclusively skeletal.[1,2] Extramedullary spread is quite unusual. After dissemination, the clinical, pathologic and laboratory findings are indistinguishable from multiple myeloma. Although a definite percentage of patients with solitary plasmacytoma of bone manifest no recurrences after treatment and have no dissemination of their disease, they should be considered as always at risk for multiple myeloma.[1,2]

MULTIPLE MYELOMA

In contrast to the low incidence of solitary plasmacytoma of bone in the jaw bones, radiographic evidence of such involvement by multiple myeloma is not uncommon and is estimated at nearly 30%.[3] The jaw lesions appear as multiple, noncorticated, small, osteolytic lesions. They vary in size from 1 to 3 mm and seldom exceed 1 cm. Confluence of the lesions is rarely seen. In up to 15% of cases of multiple myeloma, the jaw lesions may be the primary manifestation of the disease.[3] Both maxilla and mandible may be affected, but the mandible is most often the site. In the mandible, the initial lesions tend to appear in the posterior region where marrow spaces are largest and extend forward and below the mandibular canal. There is also extension up into the marrow spaces of edentulous regions and into the ramus.

EXTRAMEDULLARY PLASMACYTOMA

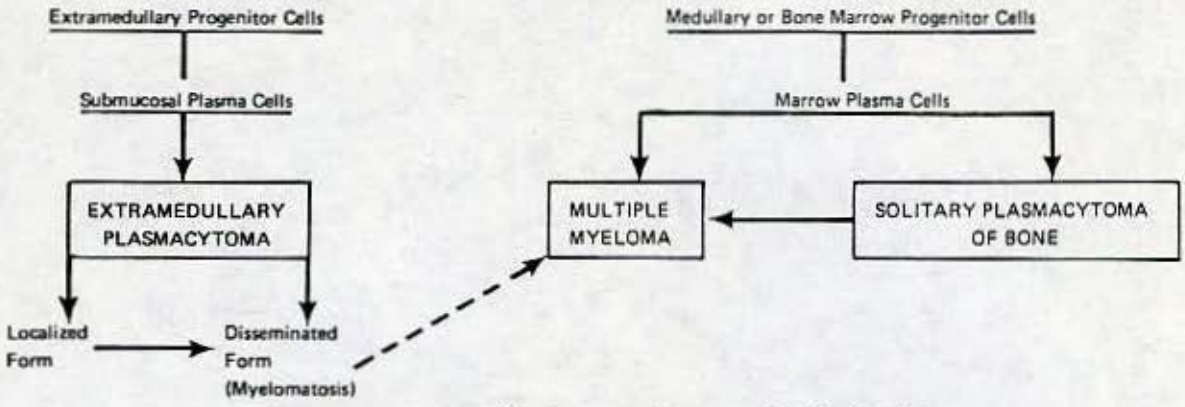
Extramedullary plasmacytoma is the term applied to plasma cell tumors which present outside of bone.[1,2,4] Tumors arising in the skeleton which have broken out through the cortex to form an associated soft tissue mass are excluded. Of all extramedullary plasmacytomas, up to 80% have been recorded as arising in the upper air passages and oral cavity.[4] They represent nearly 4% of all nonepithelial neoplasms of the nasal cavity, nasopharynx, and paranasal sinuses.[5] Arising in submucosal tissues in these sites, the plasmacytoma presents as a fleshy, yellow-gray to dark red, sessile, polypoid or pedunculated tumor. Ulceration is not frequent but underlying bone may be involved.

Between 10% to 20% of upper aerodigestive tract plasmacytomas will manifest multiple lesions in the head and neck, eg, nasopharynx and nasal cavity or larynx and pharynx.[1]

The biologic behavior of an extramedullary plasmacytoma of the upper aerodigestive tract can fall into one of several patterns: 1) localized solitary disease, controlled by surgery, radiotherapy, or both, and which does not recur or become disseminated; 2) locally recurrent disease, controlled by additional therapy; 3) aggressive, persistent, or recurrent disease producing death of the host through uncontrollable local extensions; 4) local disease with "metastatic" involvement of regional lymph nodes but without evidence of distant spread; and 5) local disease, recurrent or otherwise, followed by dissemination and development of multiple plasma cell neoplasms and/or multiple myeloma. Assessed by clinical stage, localized and controllable plasmacytomas are stage I. Stage II disease includes those tumors with local extension and/or involvement of lymph nodes. Disseminated disease is stage III. With an increase in stage, the probability of serum and urine abnormalities being detected increases. This relates to tumor mass and not to the cellular composition, since each plasmacytoma elaborates its own monoclonal proteins.[6,7]

Histologic appearance cannot be used as a reliable indicator of biologic activity.[4] The typical extramedullary plasmacytoma consists of a monocellular proliferation of plasma cells set in a very sparse matrix. Cellular and nuclear atypia may be minimal or prominent. Binucleate and trinucleate cell forms may be present and in some fields only a proximity to more definable plasma cells allows definition of the cells. Local amyloid is found in about 15% of the cases, but systemic amyloidosis is very unusual.

In the most comprehensive review to date, Wiltshaw[1] indicates that 40% of extramedullary plasmacytomas spread beyond the presenting site and its drainage lymph nodes. Of these, 81% developed lesions in bone (most often single and randomly distributed) and 62% had soft tissue and visceral de-



Proposed interrelationships of plasma cell tumors of head and neck.

posits. The spread to bone demonstrates no preference for active hematopoietic tissue, such as myeloma prefers, and is rarely as widespread or diffuse as that seen in patients with multiple myeloma.

The variable patterns of behavior of extramedullary plasmacytomas set them apart from the other plasma cell disorders, but the reasons for this are hard to find.[1,7] The low tumor burden is certainly accountable for the normal or near-normal immunoglobulins and the usual absence of detectable myeloma proteins. The predominance of IgG-containing plasma cells in the nasopharynx and upper airway may also be an ameliorating factor since myeloma patients with IgG have better therapeutic responses and survival than do patients with an IgA myeloma.[6] The reported good response to chemotherapy in patients with disseminated disease from extramedullary plasmacytomas differs from the poor survival manifested by most patients with multiple myeloma.[1] There is an overall survival rate of more than 50% at ten years for extramedullary plasmacytoma patients.[1] Finally, plasma cell dyscrasias originating from extramedullary sources tend to behave more like lymphoreticular neoplasms than multiple myeloma. The regional lymph node involvement and nodular rather than diffuse bone marrow involvement speak to that hypothesis.[1,8]

The Figure summarizes the interrelationships of the plasma cell tumors affecting the head and neck. The Figure acknowledges the possibility of evolution of extramedullary plasmacytoma to multiple myeloma but relates the differences in the dissemination pattern and better prognosis to the disorder *myelomatosis* as distinct from multiple myeloma.

SUMMARY

Neoplastic plasma cell disorders, multiple myeloma, extramedullary plasmacytoma and solitary plasmacytoma affect the head and neck with different manifestations. Multiple lytic lesions of the jaws and infrequent soft-tissue lesions characterize multiple myeloma's presence. The solitary plasmacytoma of bone is infrequent in the jaws. Wherever it occurs, it is a precursor lesion to multiple myeloma. Extramedullary plasmacytoma has several clinical and biologic forms. The most benign is the local upper airway lesion that is amenable to surgery or radiotherapy and manifests no recurrences. Approximately 40%, however, terminate in osseous and soft-tissue dissemination. The distant involvement has more characteristics of metastases than the diffuse axial skeletal involvement of multiple myeloma; to acknowledge this distribution and the apparently better prognosis, the disseminated form is called myelomatosis.

REFERENCES

1. Wiltshaw E. The natural history of extramedullary plasmacytoma and its relation to solitary myeloma of bone and myelomatosis. Medicine (Baltimore) 1976; 55:217-38.

2. Woodruff RK, Malpas JS, White FE. Solitary plasmacytoma: II. Solitary plasmacytoma of bone. Cancer 1979; 43: 2344-7.

3. Bruce KW, Royer RQ. Multiple myeloma occurring in the jaws: a study of seventeen cases. Oral Surg 1953; 6:729-44.

4. Batsakis JG, Fries GT, Goldman RT, Karlsberg RC. Upper respiratory tract plasmacytoma: extramedullary myeloma. Arch Otolaryngol 1964; 79:613-8.

5. Fu Y-S, Perzin KH. Nonepithelial tumors of the nasal cavity, paranasal sinuses & nasopharynx: a clinicopathologic study: IX. Plasmacytomas. Cancer 1978; 42:2399-406.

6. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma: correlation of measured myeloma cell mass & presenting clinical features, response to treatment, and survival. Cancer 1975; 36:842-54.

7. Woodruff RK, Whittle JM, Malpas JS. Solitary plasmacytoma: I. Extramedullary soft tissue plasmacytoma. Cancer 1979; 43:2340-3.

8. Marsch WC, Gross UM. Frequency and pathomorphology of extramedullary manifestations in plasma cell myeloma of the skeleton. Path Res Practice 1978; 163:115-27.

Case 20. Maxilla, aneurysmal bone cyst

Aneurysmal bone cysts, at any sites in bone are usually lesions of younger patients (most in the 2nd and 3rd decades). There is no sex predilection. Over 50% present in the long bones and vertebral column. The lesions are usually tender or painful and accompanied by swelling over the involved bone.

Grossly, the findings are quite characteristic. Pronounced bleeding is common and the lesion has been likened to a blood-filled sponge.

In the jaws, the lesions are preponderantly in the mandible (mandible: maxilla ratio is 2:1).

Radiographically, the bone is expanded and there may be a soap bubble or honeycomb appearance. The expansion of the bone is often eccentric. Cortical bone may be destroyed and accompanied by a periosteal reaction.

Blood-filled spaces, intervening fibrous connective tissue stroma, and multinucleated giant-cells with a patchy distribution are the histologic features. Varying amounts of hemosiderin and new osteoid and bone formation are present. The large spaces are devoid of endothelium and basement membranes. Intervening stroma is also devoid of collagen types IV and V.

At least three theories of pathogenesis prevail: (1) a persistent local alteration in hemodynamics with increased venous presence leading to an enlarged vascular bed in the transformed bone region.

Resorption of bone follows with replacement of connective tissue, osteoid and new bone formation.

(2) an exuberant attempt at repair of a hematoma of bone, similar to the central giant-cell granuloma. (3) an accompaniment of other primary lesions of bone wherein the primary lesion creates an osseous A-V fistula.

Of 48 primary aneurysmal bone cysts in the jaws reviewed by Gingell et al., approximately 75% were in patients 20 years or younger, the mean age being 16 years. Twenty-six (58%) presented in the mandible and 22 (42%) in the maxilla.

The association of other bone lesions in a tumor having characteristics of an ABC has been estimated at approximately 25%. Pathologists should always exclude the association. The following have been recorded by various authors as being associated with ABC's:

Ossifying fibroma, non-ossifying fibroma, cermentifying fibroma, osteosarcoma, giant-cell tumor, central giant-cell granuloma, fibrous dysplasia, chondroblastoma, osteoblastoma, hemangioma, chondromyxoid fibroma, sarcoma, solitary bone cyst.

El Deeb, M., Sedano, H.O., and Waite, D.E.: Aneurysmal bone cyst of the jaws. Report of a case associated with fibrous dysplasia and review of the literature. Int. J. Oral Surg. 9:301-311, 1980.

Baker, H.L., Papsidero, M.J., Batsakis, J.G., and Krause, C.J.: Aneurysmal bone cyst of the ethmoid. Head and Neck Surg. 5:177-180, 1982.

Struthers, P.J., and Shear, M.: Aneurysmal bone cyst of the jaws. (I). Clnicopathological features. Int. J. Oral Surg. 13:85-91, 1984.

Struthers, P.J., and Shear, M.: Aneurysmal bone cyst of the jaws. (II). Pathogenesis. Int. J. Oral Surg. 13:92-100, 1984.

Chambers, T.J.: The pathobiology of the osteoclast. J. Clin. Pathol. 38:241-252, 1985.

Aho, H.J., Aho, A.J., Pelliniemi, L.J., Ekfors, T.O., and Foidart, J-M.: Endothelium in aneurysmal bone cyst. Histopathology 9:381-387, 1985.

Gingell, J.C., Levy, B.A., Beckerman, T., and Tilghman, D.M.: Aneurysmal bone cyst. J. Oral Maxillofac. Surg. 42:527-534, 1984.

ANEURYSMAL BONE CYST OF THE ETHMOID

Herbert L. Baker, MD, Michael J. Papsidero, MD, John G. Batsakis, MD, and Charles J. Krause, MD

Abstract Although nearly 500 cases of aneurysmal bone cyst have been recorded in the English literature, involvement of the facial bone is uncommon. To our knowledge, this is the first case of extragnathic, facial aneurysmal bone cyst to be reported in the English literature. A left ethmoid aneurysmal bone cyst was found in a 20-year-old pregnant woman who had a 5-month history of progressive left periorbital swelling, left cystic nasal mass, progressive nasal obstruction, blurred vision, and occasional diplopia. The diagnostic evaluation included a sinus series, facial laminograms, and an EMI scan. Needle aspirates taken frequently from the intranasal cyst consisted of a dark, bloody fluid. The surgical procedure, using external rhinotomy approaches, pathologic findings, and a literature review are presented.

HEAD & NECK SURGERY 5:177–180 1982

Although nearly 500 cases of aneurysmal bone cyst have been recorded in the English literature, involvement of the facial bones is distinctly uncommon.[1] In 1979, Steidler and associates[2] recorded the 29th case. Of these, 11 patients had tumors within the maxilla and 18 patients had tumors within the mandible. To date aneurysmal bone cysts arising in other facial bones have not been reported. To our knowledge, the case presented here is the first example of extragnathic, facial aneurysmal bone cyst to be reported in the English literature.

CASE REPORT

A 20-year-old Caucasian woman in the second trimester of pregnancy presented with a 5-month history of progressive left nasal obstruction, left periorbital swelling, mild proptosis, blurred vision, and occasional diplopia. At the time of her evaluation in the department of otolaryngology, the patient was found to have a large mass involving the left nasal vault that was mucosally covered and quite firm (Fig. 1). The patient also presented with left infraorbital edema and mild proptosis. The results of examinations of the nasopharynx, oral cavity, hypopharynx, larynx, and neck were all within normal limits. Further evaluation included laminograms of the paranasal sinuses and orbits, which demonstrated erosion of the left cribriform plate, the left ethmoid cells including the lamina papyracea, and the left orbital floor (Fig. 2). An EMI scan (EMI 1005 scanner, EMI, Brandenburg, Great Britain) demonstrated apparent extension into the anterior cranial fossa. Arteriogram was performed and demonstrated no abnormality except for some tenting of the dura in the cribriform area.

A biopsy of the nasal lesion was performed, revealing a cystic mass which contained 20 ml of

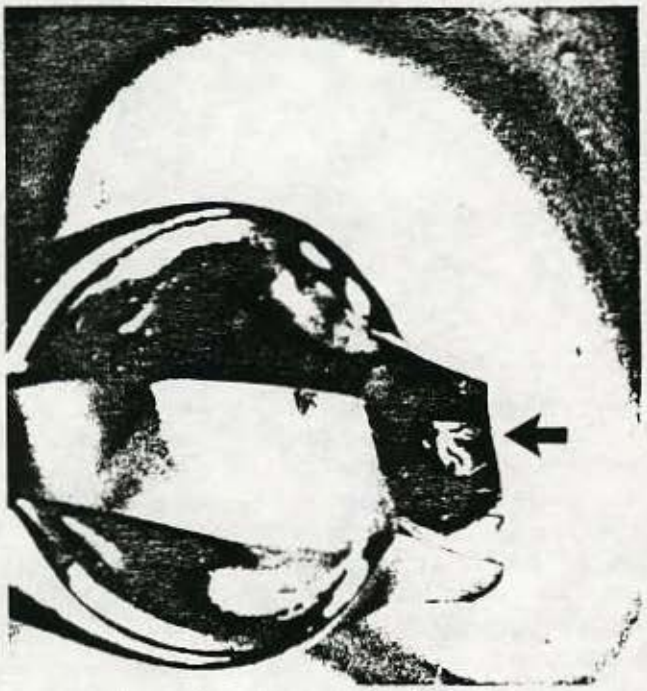


Figure 1. A large mass is seen to involve the left nasal vault

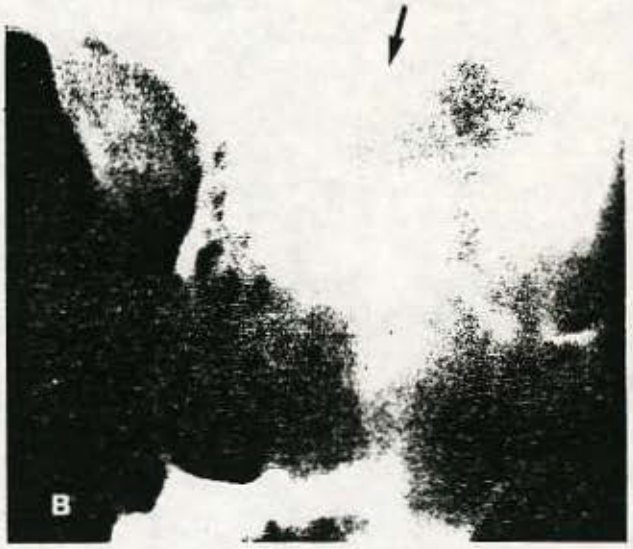


Figure 2. (A) Water's view showing left maxillary, ethmoid, and frontal sinuses. (B) Laminogram of the patient demonstrating erosion of the left cribriform plate, the left ethmoid cells (including the lamina papyracea), and the left orbital floor.

dark bloody fluid. On histologic evaluation a diagnosis of aneurysmal bone cyst was made. Due to the fact that this patient was within the second trimester of pregnancy, aspiration was employed initially in an attempt to reduce the size of the lesion. During the next few weeks it became necessary to aspirate the cyst every other day to achieve relief of symptoms. Because of this increase in the frequency of aspiration required, and because of persistent eye symptoms—blurred vision, proptosis, and diplopia—it was decided to proceed with surgical resection of the lesion. The patient was taken to the operating room where she underwent a left frontoethmoidectomy and sublabial approach to the maxillary sinus. The mass was completely removed and the patient's postoperative course was unremarkable. There was resolution of all symptoms, including the blurred vision, diplopia, proptosis, and persistent discomfort. The patient has been followed for 2 years and there is no evidence of recurrence.

GROSS AND MICROSCOPIC PATHOLOGIC FINDINGS

The surgical specimen measured 3.5 cm in diameter at the widest point, and was cystic, friable, and brown. Light microscopic examination revealed the lesion to be composed of fibrous walled channels or spaces containing blood or a serosanguinous fluid (Fig. 3). Some of the spaces were partially lined with endothelium, although the majority had no lining except for the fibrous connective tissue itself. No elastic fibers or smooth muscle tissue was demonstrable in the walls of these vascular spaces. Evidence of hemorrhage and associated foci of giant cells were irregularly distributed in the fibrous septae (Fig. 4). At the

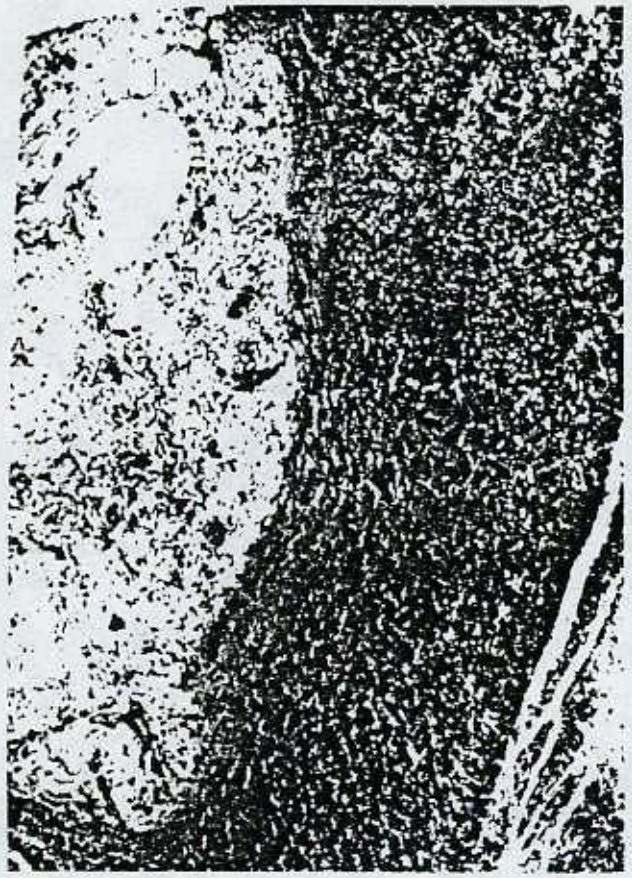


Figure 3. Low-power micrograph of the aneurysmal bone cyst showing a blood-filled space on the right that is bordered by moderately vascular fibrous connective tissue containing scattered giant cells. Hematoxylin and eosin, ×30.

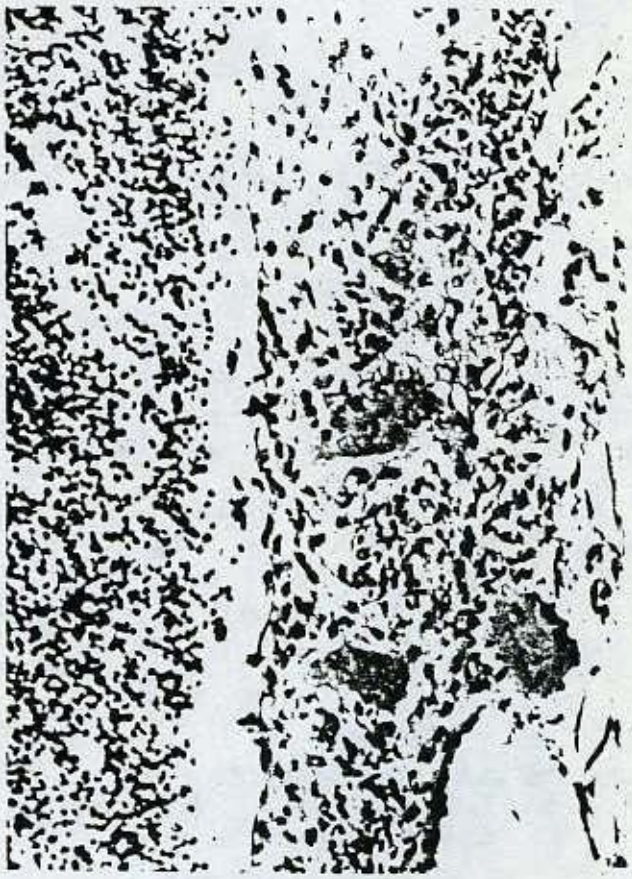


Figure 4. Micrograph of the wall of the aneurysmal bone cyst. In this field the blood-filled space is lined by a thin septum of connective tissue containing giant cells. At the right is thin newly formed bone. Hematoxylin and eosin, ×200.

periphery of the lesion, osteoid and subperiosteal bone formation was present. Multiple sections of the tumor were similar and no other definable bone tumor was identified.

DISCUSSION

The aneurysmal bone cyst is neither an aneurysm nor a true cyst. "Aneurysm" was originally used to convey the "blowout" distention of the contour of the involved bone. "Cyst" refers to the prominent dilated blood-filled channels and spaces which often lack an endothelial lining.

The lesion may present in any bone, but long tubular bones and the spine account for over 75% of the reported cases. Facial bone involvement is far less frequent, with the maxilla and mandible being the predominant sites.[3] In all sites, the lesions usually develop before the third decade of life. For lesions involving the jaws, there is an apparent predilection for females.

Although the pathogenesis of aneurysmal bone cysts remains unclear, the lesions have been clinically and histologically divided into primary and secondary forms.[1-3,5] Secondary aneurysmal bone cysts are those found in association with a coexisting bony lesion, either benign or malignant. It is important to recognize the secondary form of disease not only because the coexisting disorder may be obscured or missed but also because of potential pathogenetic relationships. The fact that some studies have demonstrated that nearly one third of aneurysmal bone cysts manifest a synchronous definable tumor or disorder of bone, has led some authors to question whether the aneurysmal bone cyst is itself a clinicopathologic entity.[3] The substantial number of aneurysmal bone cysts that develop without apparent associated lesions suggests that primary aneurysmal bone cysts do occur and are deserving of separate status. We concur with Unni and associates,[6] that the diagnosis of a primary cyst may be made only when the histologic criteria are fulfilled and no

other coexisting lesion is found. If there is an underlying lesion that provides a primary diagnosis and indicates biologic behavior, we merely indicate that aneurysmal bone cyst-like areas are present.

According to the above classification, the lesion in this patient was a primary aneurysmal bone cyst. No histologic evidence of another bone lesion was found. An association with pregnancy has not been reported.

Radiographic features of an aneurysmal bone cyst are characteristic, although not diagnostic. In general, and irrespective of location, the involved bone is expanded by a solitary, lytic, and variably cystic lesion. All lesions manifest cortical thinning, and some also demonstrate cortical bone erosion. The periphery of the lesion is, as a rule, faintly outlined by a delicate rim of periosteal new bone formation. An associated soft tissue mass and fracture may also be present. Angiograms are helpful in determining the extent of this vascular lesion but are not pathognomonic.

The recurrence rate after various forms of treatment for primary extrafacial aneurysmal bone cysts is significant, ranging from 21% to 44%.[3,7] For currettage, the most frequently applied treatment technique, the rate is even higher.

Less tangible data are available regarding oral and facial lesions,[8,9] since far fewer of them have been reported, and follow-up on the reported cases has been short; however, it appears that recurrence among maxillofacial lesions has been less of a problem.[8,9] Treatment usually requires only complete local resection of the involved structures. In one series reported by Kane of 10 lesions involving the maxilla, 8 were locally resected, and only 2 required a partial maxillectomy.[8]

Patients considered at risk for recurrence include not only those with incomplete removal of their tumors but also those in which the tumor manifests a mitotic index of ≥ 7 per 50 fields (×570).[7]

REFERENCES

1. Bonakdarpour A, Levy WM, Aegerter E: Primary and secondary aneurysmal bone cyst: a radiological study of 75 cases. *Radiology* 126:75–83, 1978.
2. Steidler NE, Cook RM, Reade PC: Aneurysmal bone cysts of the jaws: A case report and review of the literature. *Br J Oral Surg* 16:254–261, 1979.
3. Biesecker JL, Marcove RC, Huvos AG, Mike V: Aneurysmal bone cysts. A clinicopathologic study of 66 cases. *Cancer* 26:615–625, 1970.
4. Buraczewski J, Dabska M: Pathogenesis of aneurysmal bone cysts. Relationship between aneurysmal bone cyst and fibrous dysplasia of bone. *Cancer* 28:597–604, 1971.
5. Levy WM, Miller AS, Bonakdarpour A, Aegerter E: Aneurysmal bone cyst secondary to other osseous lesions. Report of 57 cases. *Am J Clin Pathol* 63:1–8, 1975.
6. Unni KK, McLeod RA, Dahlin DC: Conditions that simulate primary neoplasms of bone. *Pathol Annu* 15:91–131, 1979.
7. Ruiter DJ, vanRijssel ThG, van der Velde EA: Aneurysmal bone cysts. A clinicopathological study of 105 cases. *Cancer* 39:2231–2239, 1977.
8. Kane KJ: Aneurysmal bone cyst of maxilla. *Ann Otol* 88:217–221, 1979.
9. Oliver LP: Aneurysmal bone cyst. Report of a case. *Oral Surg* 35:67–76, 1973.

Case 21. Floor of mouth, extraosseous osteogenic sarcoma

The head and neck region is an unusual site for these uncommon neoplasms. Approximately 5% of all extraosseous osteogenic sarcomas originate in the soft tissues of the face and neck. The sarcomas may arise after a latent period following radiotherapy. The majority arise de novo. The sarcomas are very aggressive and lethal with an average 5-year survival of 15.6%.

Origin is in the deep somatic soft tissues, usually in relation to fascia or an aponeurosis. By definition, they must not have radiologic, clinical or pathologic relationships to osseous structures.

Site predilection is for the soft tissues of the lower extremity, thigh and buttocks. Extraosseous osteosarcoma almost always presents in patients who are more than 40 years of age.

By 1985, seven extraosseous osteogenic sarcomas have been recorded in the head and neck.

Recurrences are frequent and nearly always presage distant spread and death. Sordillo et al record a 94% recurrence rate; most of the recurrences presenting within 2-years of primary treatment. Almost 80% of patients die within 2-3 years after diagnosis with an average 5-year survival of 15.6%. All histologic types are equally deadly.

Sordillo, P.P., Hajdu, S.I., Magill, G.B. and Golbey, R.B.: Extraosseous osteogenic sarcoma. A review of 48 patients. Cancer, 51:727-734, 1983.

Rao, V., Cheng, A. and Didolkar, M.S.: Extraosseous osteogenic sarcoma: Clinicopathologic study of eight cases and review of literature. Cancer, 41:1488-1496, 1978.

Allan, C.J., and Soule, E.H.: Osteogenic sarcoma of the somatic soft tissues. Clinicopathologic study of 26 cases and review of the literature. Cancer, 27:1121-1133, 1971.

Wurlitzer, F., Ayala, A.G., and Romsdahl, M.: Extraosseous osteogenic sarcoma. Arch. Surg, 105:691-695, 1972.

Extraosseous Osteogenic Sarcoma*

Anatomic Site of Origin	Number of Cases
Thigh, buttocks, lower extremity	78
Upper extremity	20
Trunk	13
Head and Neck	7
Retroperitoneum	6
Breast	2
	125

*From data presented by Wurlitzer et al, Allen and Soule, Rao et al and Sordillo et al.

Extraosseous Osteogenic Sarcoma in the Head and Neck

Anatomic Site	No. Cases	Age of Patients	Comment
Orbit	2	11yrs., 10yrs.	Both sarcomas arose after irradiation of retinoblastoma. Both patients died of extensive local recurrence within 1yr. of diagnosis.
Soft tissue of chin	2	48yrs., 48yrs.	One sarcoma arose after irradiation. Both patients died of local recurrence, 9 mos. and 2½ yrs. after diagnosis.
Soft tissue of face	2	41yrs., no information	Patient with information, alive and well 12½yrs.
Parotid gland	1	73yrs.	Present case.

Case 22. Chondrosarcoma, low-grade (larynx)

Non-epithelial neoplasms of the larynx make up no more than 1% of the malignancies affecting that structure.

Lesions composed of cartilage fall into three groups; (1) chondromatous metaplasia, (2) chondroma and (3) chondrosarcoma.

Among the non-neoplastic cartilage-containing lesions of the larynx are the chondrometaplastic nodules. Chondrometaplasia of the larynx does not arise from hyaline cartilage and does not have the typical lobular pattern of hyaline cartilage.

Chondrometaplasia occurs in two settings: (a) asymptomatic and found at necropsy where they are smaller than 2 mm and preponderantly in the region of the false cord, and (b) larger (usually less than 1 cm), symptomatic nodules that occur in the vocal cords, epiglottic and rarely, in the ventricle. Patients whose ages range between 14 and 98 years may have them.

Chondrometaplasia has a predilection for the posterior and midportions of the glottis where it must be distinguished from the normal vocal process of the arytenoid. Like chondrometaplasia, the vocal process is also composed of elastic cartilage, but, unlike chondrometaplasia, it is a well circumscribed nodule.

Size, clinical setting and indistinct margins of a chondrometaplasia serve to separate the lesion from chondrosarcomas and chondromas.

Both chondroma and chondrosarcoma share essentially the same biologic course. The eventual outcome of lesions initially labeled

chondroma is not significantly different from those identified as chondrosarcoma at the onset. The tumors arise from hyaline cartilage and show no evidence of elastic tissue. There is a striking predilection for chondrosarcomas to arise in the region of the cricoid cartilage (70-75%), usually in the posterior or posterolateral areas. Origin from the thyroid cartilage follows distantly and an arytenoid origin is rare.

Males are affected most and the median age at onset is 63 years. The tumors grow slowly and most of the symptoms are those of a slowly expanding tumor. On examination, most patients have a discrete endolaryngeal mass that is smooth and sessile; the mass is covered with normal mucosa.

Chondrosarcomas of the larynx are nearly always low-grade (grade I and II). The criteria used are the same as those used in cartilaginous lesions elsewhere in the body; increased cellularity, presence of double-nucleated cells, and atypia of the nuclei.

Chondrosarcomas of the larynx rarely metastasize and their slow course allows conservative management if the size and site of the chondrosarcoma allow.

Most chondrosarcomas are removed by a laryngofissure approach. A few are extralaryngeal and can be removed through the neck. In approximately one fourth of patients a total laryngectomy will be necessary. In all cases, the oncologic principle of including margins of normal tissue should be followed.

Hill, M.J., Taylor, C.L., and Scott, G.B.D.: Chondromatous metaplasia in the human larynx. Histopathology, 4:205-214,1980.

Neel, H.B., and Unni, K.K.: Cartilaginous tumors of the larynx: a series of 33 patients. Otolaryngol. Head and Neck Surg. 90:201-207, 1982.

Lavertu, P., and Tucker, H.M.: Chondrosarcoma of the larynx. Case report and management philosophy. Ann. Otol. 93:452-456, 1984.

Hyams, V.J., and Rabuzzi, D.D.: Cartilaginous tumors of the larynx. Laryngoscope 80:755-767, 1970.

Escher, A., Escher, F., and Zimmerman, A.: Zur Klinik und Pathologie chondromatoser Tumoren des Larynx. HNO 32:269-285, 1984.

Case 23. Vocal cords, sarcomatoid carcinoma

This case was seen by me in consultation prior to the seminar. In this event, I violated my own rules for such lesions. These are: (1) multiple sections are necessary to find carcinoma or abnormal mitoses, (2) the diagnosis of sarcomatoid carcinoma is to be made when carcinoma is found or when there is historical evidence of a carcinoma at the site.

Subjectively the original material was interpreted by me as a reactive laryngeal polyp containing pleomorphic cells considered to be the atypical, yet benign stromal cells found in antro-choanal polyps and in certain polypoid lesions of the bladder and female external genital tract.

Cytokeratins were not found in the original material. The seminar set forced a change in diagnsis because of the several markedly atypical mitoses in the stroma-like cells. These mitoses, in my opinion are foreign to reactive lesions.

The diagnosis is changed to sarcomatoid carcinoma. Because of its polypoid configuration, laryngeal location and absence of definable carcinoma, it is likely that conservative laryngeal surgery can control the neoplasm.

The accompanying reprint outlines the difficulty with these peculiar lesions and also gives a discussion of several fibrous proliferations in the head and neck.

THE PATHOLOGY OF HEAD AND NECK TUMORS: SPINDLE CELL LESIONS (SARCOMATOID CARCINOMAS, NODULAR FASCIITIS, AND FIBROSARCOMA) OF THE AERODIGESTIVE TRACTS, PART 14

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and DONALD R. HOWARD, MD

Abstract: The term spindle cell lesion, or tumor, is a purely descriptive one and if applied without further qualification is meaningless as a guide to therapy and prognosis. The three lesions presented in this report—sarcomatoid carcinomas, nodular fasciitis, and fibrosarcoma—serve to illustrate this point. One, the sarcomatoid carcinoma, is an epithelial malignancy in which the majority of the sarcoma-like spindle cells are believed to be variants of the epithelial cells. Nodular fasciitis, a self-limited and benign soft tissue lesion, is composed principally of myofibroblasts. Primarily an extramucosal lesion, it presents a pseudosarcomatous microscopic appearance. Fibrosarcomas represent the other end of the spindle cell lesion spectrum in that they are soft tissue malignancies of fibroblastic origin. Clinical, pathologic, and biologic implications of these lesions when they arise in the mucosae of the upper aerodigestive tracts of the head and neck are presented.

HEAD & NECK SURGERY 4:499–513 1982

A variety of spindle cell lesions occurs in the head and neck. Some are neoplastic; others are peculiar responses to injury of known and unknown cause. The majority are tumors of the somatic soft tissues; far fewer occur in the visceral (mucosal) compartments. When they do, the diagnostic and therapeutic decisions related to them are more complex than for their peripheral counterparts. Three lesions illustrate this complexity. The first, sarcomatoid carcinomas, likely represent the most challenging surgical pathologic problem of all the spindle cell lesions. Nodular fasciitis, the second lesion, is unusual in the mucosal surfaces, but it too can lead to diagnostic and therapeutic misadventure. The third, true fibrosarcoma, is so uncommon in these sites that it is subject to a variety of histopathologic interpretations.

SARCOMATOID CARCINOMA

The tumors variously named pseudosarcoma, pseudosarcomatous squamous cell carcinoma, sarcomatoid squamous cell carcinoma, pseudosarcoma associated with squamous cell carcinoma, pleomorphic carcinoma, metaplastic carcinoma, and epidermoid carcinoma-spindle cell variant can occur in any squamous-lined surface of the

Figure 1. Gross appearance of a sarcomatoid carcinoma at the anterior commissure of the larynx.

body.[1] In the head and neck no mucosal region is spared, but the oral cavity and larynx are the predominant sites of involvement.

Whenever the lesions are encountered they promote controversy. In dispute are: (*1*) their cellular composition and histogenesis, (*2*) their biologic course and prognosis, and (*3*) management.

For legitimate inclusion, the tumors must manifest a bimorphic histologic appearance: definable squamous cell carcinoma (in situ or invasive) and an underlying or adjacent atypical stromal component composed of fusiform cells often having a fibrosarcoma-like appearance. The atypical stroma dominates and overshadows the carcinoma in every case. The carcinoma may be elusive because of the attendant surface necrosis and its demonstration often requires multiple sections and diligent examination. The most fertile areas for its discovery are the depths and margins of the mass.[1,2] On occasion, carcinomatous foci are within the central parts of the stromal proliferation.

The typical tumor is a rapidly growing, usually polypoid and sometimes bulky mass (Figs. 1 and 2). They may be as small as 1.0 cm or as large as 6 to 8 cm. A history of prior irradiation is not uncommon. Patients are usually male and in their sixth or seventh decade. Polypoid lesions are nearly always friable with surface necrosis. Occasionally bits of the tumors appear in expectorations. A smaller number of the tumors are sessile or ulcero-infiltrative.

Figure 2. Polypoid sarcomatoid carcinoma of the supraglottic larynx. The surface is denuded of epithelium and replaced by a granulation tissue. This neoplasm contained well-differentiated squamous cell carcinoma at the base of the exophytic mass. Hematoxylin and eosin ×18.

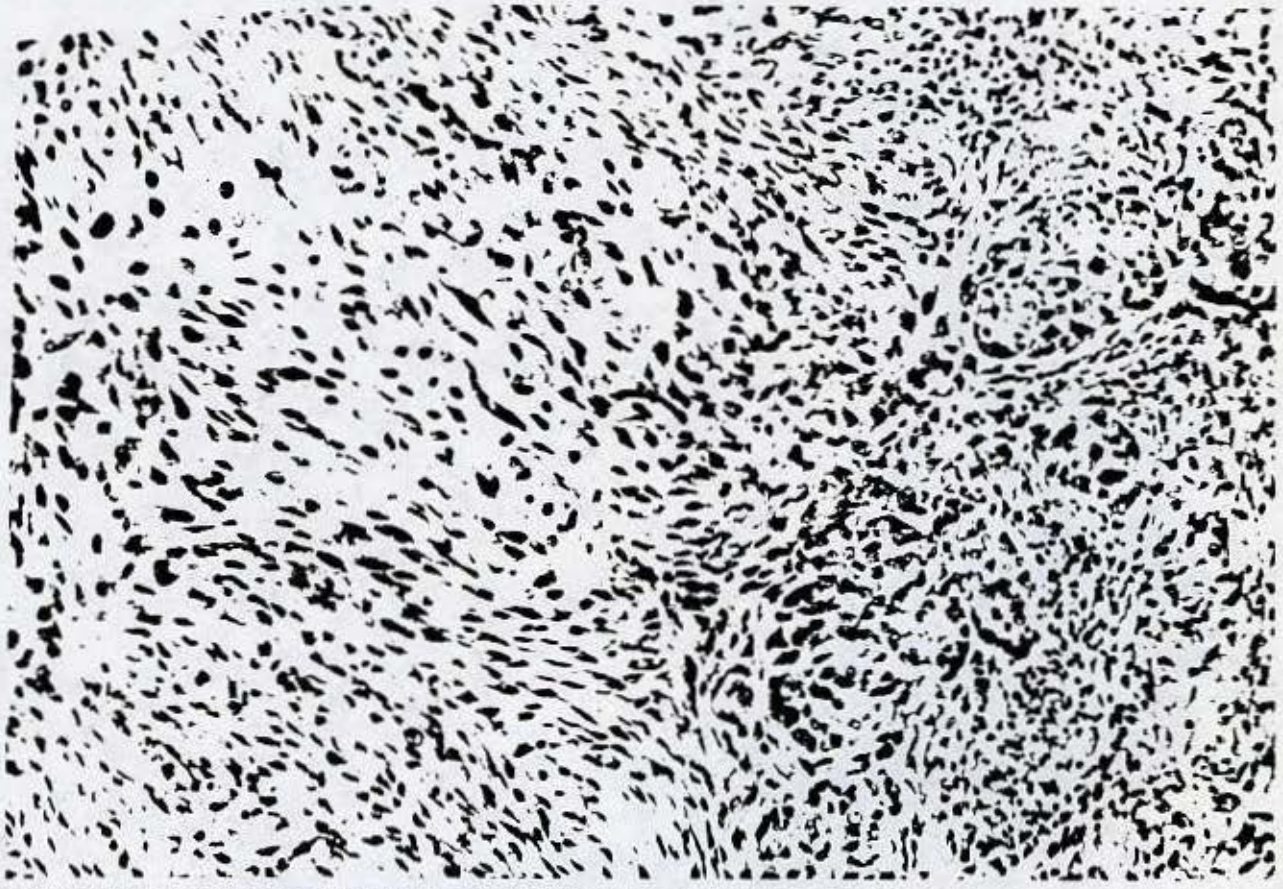

Figure 3. Poorly differentiated adenocarcinoma of the larynx (right) lies next to and is intermingled with sarcomatoid stromal cells. Hematoxylin and eosin ×200

Any region of the oral cavity may be the primary site of involvement. The vermilion part of the lower lip is apparently an area of predilection.[3] This is followed by the tongue and alveolar ridge or gingivae. In the pharynx, the pyriform sinus appears to be a preferred site.[4] The nasal cavity and maxillary antrum have been the sites cited most often in the sinonasal tract.[5] The subglottic larynx is an unusual location but the true cords and the supraglottic larynx are predominant sites.[2,6]

An atypical stromal accompaniment, sufficient to qualify as "pseudosarcomatous," may be seen rarely with glandular malignancies of the larynx (Fig. 3). It is with squamous cell carcinoma, however, that these peculiar tumors are inexorably linked. The attraction and fascination of the spindle cell component have detracted from definition of the histologic grade of the carcinomas in most reports. Our personal experience with 13 of these lesions indicates the squamous cell carcinomas have usually been well differentiated or even verrucous (Fig. 4). When specifically recorded by other authors, a similar pattern is noted.[7-9] Only a few are poorly differentiated lesions. Light microscopic "transition zones" between the carcinoma and spindled areas have been described, but sometimes this is tenuously illustrated, and other reported tumors do not manifest this finding.[1,7-10]

Cellular Composition. The differential diagnosis of spindle cell tumors is one of the most difficult tasks facing the surgical pathologist. In nonvisceral soft tissues, the task is moderately ameliorated. Traditional aids include classical histochemical techniques which are designed to identify the stromal components of the tumors (reticulin stains, van Gieson and trichrome methods for collagen and alcian blue for mucopolysaccharides, among others). Too often, however, even after careful evaluation doubt remains about the correctness of classification. Electron microscopy, particularly of tumors of somatic soft tissues, plays an important role in refining the diagnosis.

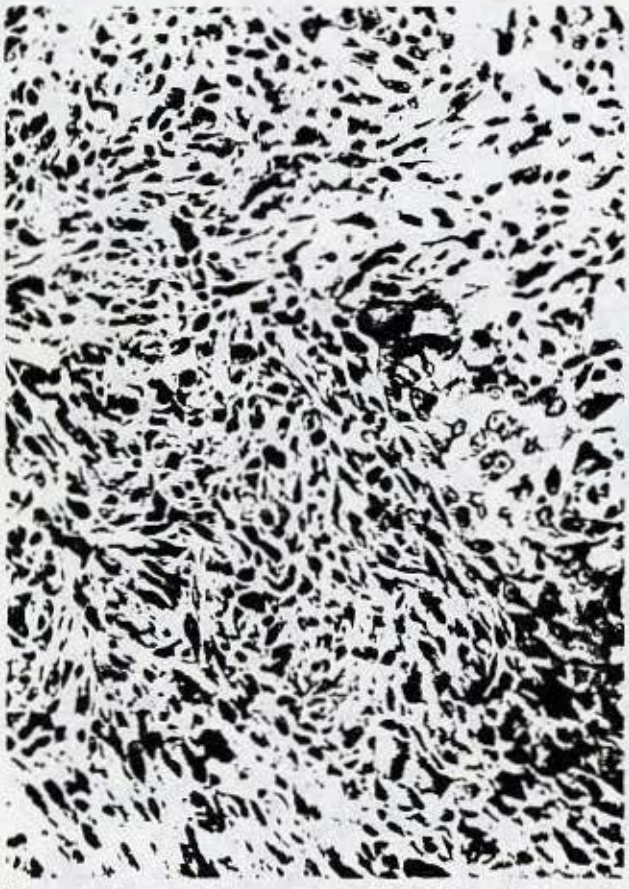

Figure 4. Sarcomatoid squamous cell carcinoma of the larynx. Fragmented, well-differentiated squamous cell carcinoma blends with neoplastic spindle cell component. Hematoxylin and eosin ×200.

Table 1. Postulated origin of spindle cells in pseudosarcomas

Authors' method of study	Conclusions
Lane[4] light-optic	Mesenchymal-benign stromal reaction
Goellner et al.[7] electron-optic and histochemical	Mesenchymal-benign stromal reaction
Hyams[2] light-optic	Epithelial-spindle cell carcinoma
Matsusaka et al.[14] light-optic	Epithelial-spindle cell carcinoma
Kleinsasser and Glanz[11] light-optic	Epithelial-spindle cell carcinoma
Someren et al.[16] electron-optic	Epithelial-spindle cell carcinoma
Battifora[13] electron-optic	Epithelial-spindle cell carcinoma
Feldman and Barr[15] electron-optic	Epithelial-spindle cell carcinoma
Lichtiger et al.[10] electron-optic	Epithelial-spindle cell carcinoma

For the lesions in question, however, the limitations are greater. Neither histochemistry nor electron-optic study have completely clarified the histogenesis, let alone cellular composition, of the tumors.[1,11,12] In short, these studies into the nature of the spindle cells have not been conclusive and have prompted declarations ranging from statements that the cells represent a mesenchymal metaplasia of malignant epithelial cells[13] to statements that they represent nothing more than an atypical, benign stromal reaction.[7] Table 1 lists the various conclusions on the origin of the spindle cells in pseudosarcomatous tumors of the upper aerodigestive tracts. Although the majority of investigators[2,10,11,13–16] consider the cells to be metaplastic epithelial cells, this interpretation is not uniform. Thus, we are left with the following: (*1*) The tumors are not a homogeneous class of neoplasms; (*2*) microscopic (light and electron-optic) evaluations and interpretations are not without varying degrees of subjectivity; (*3*) there are inherent and irreducible sampling limitations to any fine-structural analysis; (*4*) electron microscopy of these tumors is of probable diagnostic value only when it positively demonstrates epithelial features in the spindle cells; and (*5*) electron microscopy cannot be expected to decide the issue because it has been shown that squamous cell carcinomas can undergo a transformation that renders them nearly indistinguishable from sarcoma even at the ultrastructural level.

By light microscopic magnification, the sarcomatoid parts of the tumors present a rather consistent, but certainly not constant, appearance. Whether polypoid or ulcero-infiltrative, the cellular density is less at the denuded surface, where there is usually a myxoid zone containing spindle cells, inflammatory cells, and newly formed blood vessels. Beneath the myxomatous area, the cellular density is increased and presents a variety of histomorphologic patterns: fasciculated, myxomatous, or streaming (Fig. 5). The amount of stromal collagen is quite variable and ranges from almost none to abundant (Fig. 6). The fasciculated or interwoven pattern is most common and is composed of highly cellular groups of elongated bipolar cells in a parallel, interwoven alignment. Myxoid zones show prominent intercellular spaces and the cells are more stellate and pleomorphic here (Figs. 7 and 8). Usually one pattern dominates, but in all of the tumors there is an admixture of growth patterns.

Figure 5. Spindle cell sarcomatoid squamous cell carcinoma of the larynx dominates this microscopic field. Identifiable malignant epithelial cells are present on the right. Hematoxylin and eosin ×200

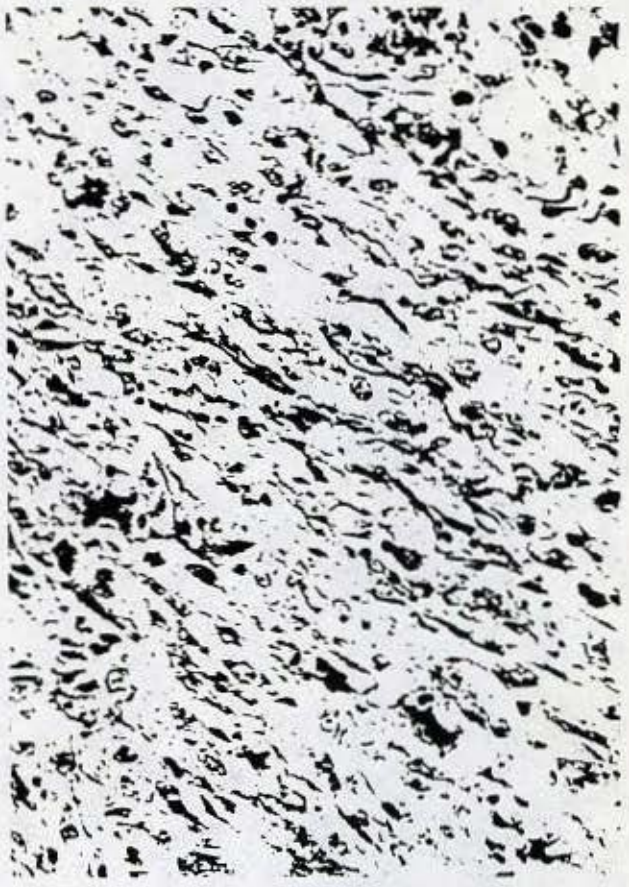

Figure 6. Epithelioid spindle cells in a sarcomatoid carcinoma of the larynx. Note the atypical mitoses. Hematoxylin and eosin ×210

The predominant cells are mainly plump, elongated, or round and may appear epithelioid. Cellular and nuclear pleomorphism may be marked or not especially notable. Mitoses are usually easy to find and atypical division figures may be common. Other cells have an ill-defined cytoplasmic margin and a foamy cytoplasm. Multinucleate foreign body-type giant cells can usually be found. Cells with an apparent phagocytic nature are scattered about and some of these large histiocytic cells contain brightly eosinophilic globules within their cytoplasm. Metaplastic osteoid, bone and cartilage may be seen (Fig. 9). These are found most often in lesions that have received prior irradiation. In the deep portion of the lesion the stromal cell-host interface is either blunt or finger-like.

The relationship between sarcomatoid tissue and definable carcinoma varies. In some tumors, there are apparent transitional or merging foci in which the cell types appear to be one; in others, islands of carcinoma are demarcated but surrounded by spindle cells.

At one part of the histologic spectrum exhibited by the sarcomatoid tissue (i.e., pronounced cellular pleomorphism, marked cellularity, mitoses, and epithelioid character of the cells) a diagnosis of malignancy is fulfilled. At another extreme, the stromal maturity, collagen formation, and few mitoses suggest a response to injury. Intermediate forms are numerous and in any tumor several patterns may be present.

If the foregoing serves as a diagnostic limitation and source of frustration for the surgical pathologist, where does it leave the surgeon? One must first consider statistical probability. Fibrosarcomas or other fibrosarcomatous tumors (neurogenous sarcoma, synovial sarcoma, fibrous histiocytoma) are not common in the upper aerodigestive tracts. Ferlito[17] ranks sarcomas among the rarest of primary neoplasms of the larynx. Of 9,119 malignant laryngeal lesions,

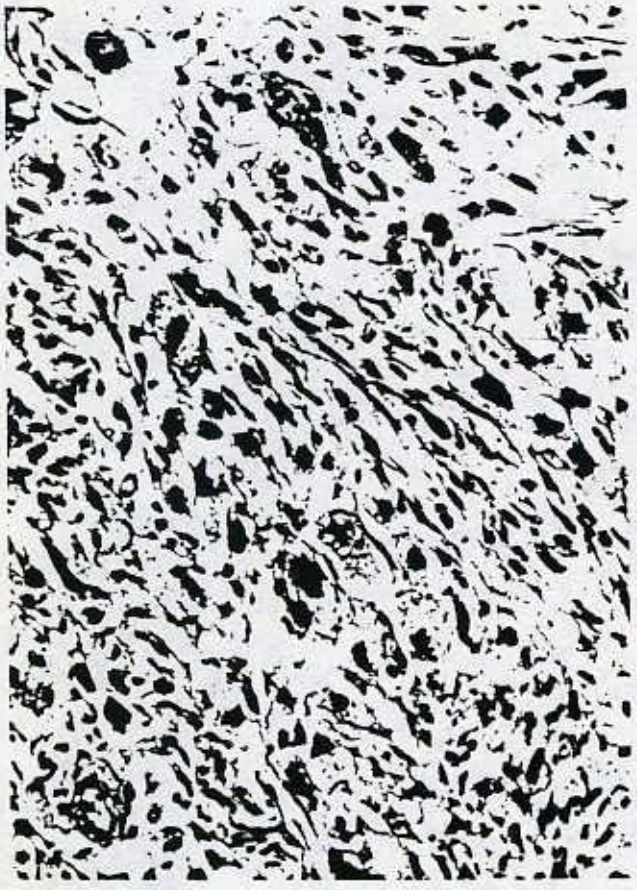

Figure 7. Pleomorphic spindle and histiocytoid cells in a sarcomatoid carcinoma of the larynx. Hematoxylin and eosin ×210

Figure 8. Higher power of the cells shown in Figure 7. Note the stellate appearance of the cells, their vacuolated cytoplasm and bizarre nuclei, and the absence of collagen. Hematoxylin and eosin ×400

only 29 (0.3%) were classified as sarcomas. First, the low frequency demands the questioning of a pathologic diagnosis of fibrosarcoma. Second, the surgeon and pathologist must exclude, as best they can, the possibility of an accompanying epithelial malignancy.

Prognostic Indicators. Because of the existing ambiguity over the cellular constituency in these tumors, authoritative statements on their biologic course, management, and prognosis abound. Some authors consider gross polypoid or pedunculated lesions to have a good prognosis, regardless of histologic findings.[18] For tumors with any other configuration, the outlook is poorer. This has been denied by other investigators who claim the most important modifier is the histologic grade of the accompanying squamous cell carcinoma.[19] In like manner, Lane,[8] Sherwin et al.[20] and Grigg et al.[21] consider the sarcomatoid mass to be least important, with prognosis to be related to the size and location of the carcinoma instead. The size and grade of the carcinoma have not been established as significant indices by others.[3,9]

Leventon and Evans[9] and Evans and Smith,[22] acknowledging the fallibility of microscopic evaluation of the spindle cells, have opted for the depth of invasion by the stromal component as the principal prognostic indicator for these lesions (Fig. 10). Dividing sarcomatoid carcinomas into superficial and invasive types, Leventon and Evans[9] record striking differences in biologic behavior, i.e., no patient with a superficial tumor died as a result of their disease, whereas 9 of 10 patients with invasive tumors died, usually after only a short time. Metastases to cervical lymph nodes were nearly limited to the invasive tumors. Invasive tumors were those in which the sarcomatoid lesional tissues extended into muscle, minor salivary tissues, or bone. Those tumors that did not involve these structures were classed as superficial. It is important to note that predictions on invasiveness could not be made on the

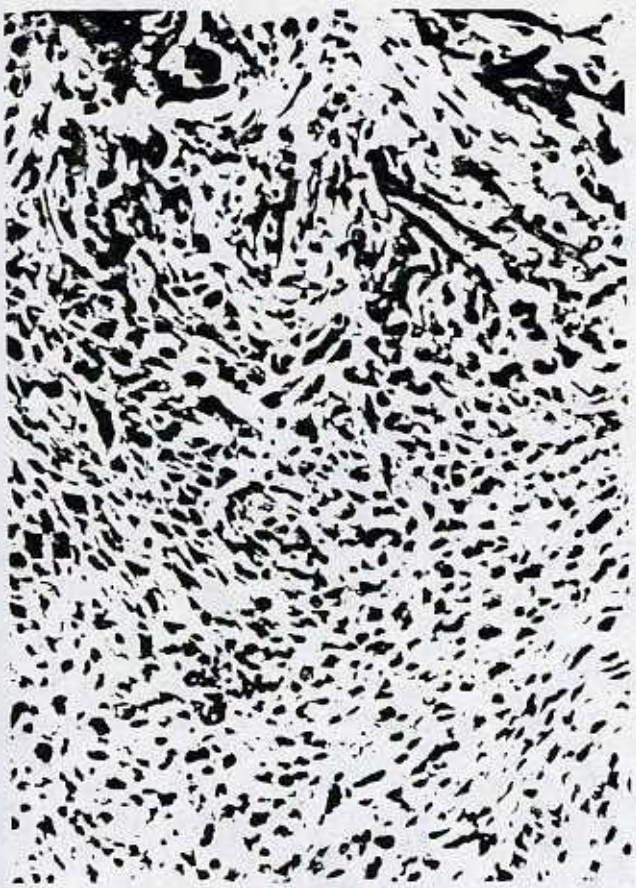

Figure 9 Sarcomatoid carcinoma of the larynx. Fine osteoid spicules are present in the upper right. Note also the histiocytoma-like appearance of the "stroma." Hematoxylin and eosin ×200

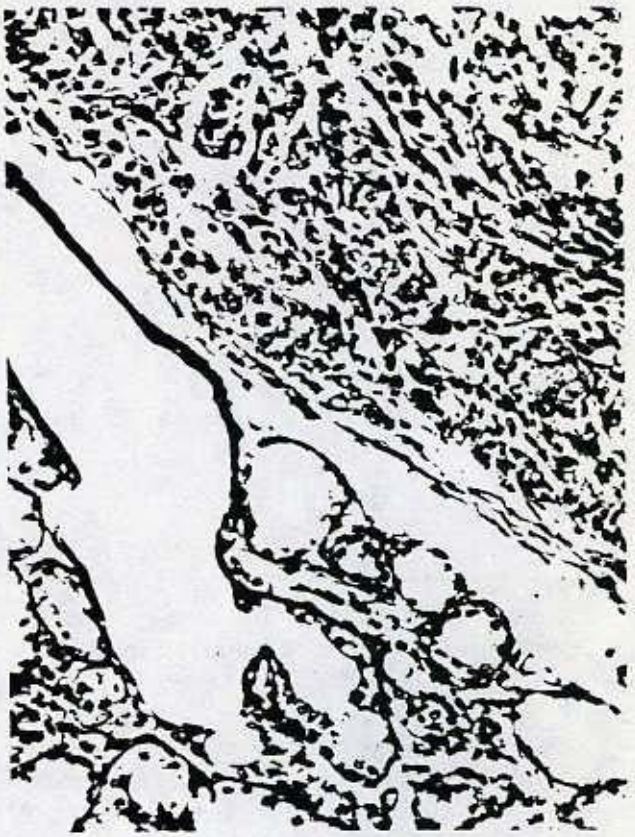

Figure 10 Sarcomatoid carcinoma of the buccal mucosa. The neoplasm has extended down to the level of the minor salivary glands. Hematoxylin and eosin ×190

basis of gross appearance, i.e. polypoid or nonpolypoid. Ellis and Corio[3] agree the gross appearance of a tumor cannot be used to significantly signal the degree of invasion shown on microscopic examination. These workers, however, did not find a correlation between the depth of invasion and prognosis.

Biologic Course. From pathogenic, etiologic, and microscopic standpoints, these tumors remain enigmatic. On an empirical basis, however, the tumors in aggregate demand therapeutic respect. When acceptance of tumors is restricted to those showing a definable carcinoma, they are quite lethal (Table 2).[2-7,9,18,23] An apparent modifying influence on mortality is suggested in Table 3. The data indicate the sinonasal tract and oral cavity harbor the more deadly tumors.[2-7,9,18,23] Ellis and Corio,[3] studying only oral sarcomatoid carcinomas, found the mean survival of patients who died of their disease to be under 2 years. In the larynx, the overall mortality secondary to persistent disease, and with at least 3 years follow-up, was 32% in the review by Lambert et al.[24] The fatal cases represented 24% of the glottic lesions and 44% of both supraglottic and hypopharyngeal lesions.

Death in the patients is related to uncontrolled local disease and regional or distant metastases. The metastatic rate in 166 cases of sarcomatoid carcinomas (oral cavity, sinonasal tract, larynx, and esophagus) was 45/166 or 27%.[3,5,6,9,14,24] Tumors in the oral cavity have a higher frequency of metastasis (24 of 65, or 37%).[3,9] Although the rate of metastases from the larynx is lower, those of the supraglottis exceed those of the glottis by a ratio of 2:1 (15% vs 30%).[24] Regional lymph nodes are the principal metastatic foci.

The majority of the metastatic deposits are carcinomatous (epithelial) only, but purely sarcomatoid or mixed metastases also occur. In a review of 21 cases with metastases from laryngeal primary lesions, it was found that 10 were epithe-

Table 2. Lethality of sarcomatoid carcinomas

Authors	Site	No. of patients	No. of patients (%) dead (with or because of disease)
Ellis & Corio[3]	Oral cavity	45	25
Leventon and Evans[9]	Oral cavity	8	7
Howell et al.[5]	Sinonasal tract	13	10
Randall et al.[6]	Larynx	7	2
Appleman and Oberman[10]	Larynx	11	7
Goellner et al.[7]	Larynx,	25	2
Hyams[2]	Larynx, pyriform sinus	20	8
Friedel et al.[4]	Larynx, pharynx	8	0
Osamura et al.[23]	Esophagus	17	4
Total		154	64 (42.2%)

lial, four were sarcoma-like, and six were mixed (1 case was not described).[24] Metastases from 24 oral cavity tumors were sarcomatous in 8 cases and carcinomatous in 16.[3,9]

Therapy. Given the unsettledness over histopathologic diagnosis, it is to be expected that guidelines for the therapy of these tumors are not well formulated. On one issue, there is a fair degree of acceptance. Although the number of patients who have been primarily treated with radiation therapy is not large and variable doses have been used, current evidence suggests it is not very effective at any site of origin of the tumors.[2,3,24] In the larynx and hypopharynx, there is a high local recurrence rate (12 of 14 tumors) and the literature records only one long-term survivor treated solely with radiation therapy.[24] Five of six patients treated solely by irradiation for their sarcomatoid carcinomas of the sinonasal tract died 6 to 30 months after diagnosis (mean survival, 15.8 months).[5] The failure of radiation therapy is also echoed by Ellis and Corio,[3] who indicate that 4 of 5 patients with oral lesions so treated died of their disease.

The effectiveness of surgical removal is somewhat better, but substantiation of this from the literature is not easy because the excisions reported have ranged from conservative to radical and clinical staging has either not been done or has not been applied uniformly. Lambert et al.[24] found that, including cases of salvage laryngectomies, and after radiation and local resection failures, partial or total laryngectomy afforded at least a 3-year disease-free interval in 9 of 9 T1 or T2 laryngeal sarcomatoid carcinomas. During a follow-up time ranging from 8 months to 11 years for 32 patients with oral tumors treated by surgical excision alone or with radical neck dissection, Ellis and Corio[3] indicate that 9 died of their disease and 9 were alive without residual or recurrent tumor.

Local resection of a sarcomatoid carcinoma, particularly for polypoid or pedunculated ones of the larynx, has occasionally yielded long-term survival. The overall high recurrence rate and mortality and nonreliability of gross configuration, however, would indicate that conservative local removal should be abandoned. In fact, classifying these lesions as polypoid or otherwise may be of importance only for glottic tumors.[24] Polypoid glottic lesions appear to have a more favorable prognosis (90% overall 3-year survival) but supraglottic, hypopharyngeal, sinonasal, and oral tumors do poorly regardless of their gross appearance.[24]

Table 3. Lethality of sarcomatoid carcinomas as modified by anatomic site of origin *

Anatomic site	No. of cases	Lethality (%)	Time to death
Oral cavity	53	32 (60)	1 mo–6 yr
Sinonasal tract	13	10 (77)	6–30 mo
Larynx	65	22 (33.8)	4 mo–2 yr

*Compiled from data by Hyams,[2] Ellis et al.,[3] Friedel et al.,[4] Howell et al.,[5] Randall et al.,[6] Goellner et al.,[7] Leventon et al.,[9] Appleman et al.,[10] and Osamura et al.[23]

Table 4. Pseudosarcomas: a classification

Sarcomatoid (pleomorphic or metaplastic) carcinoma	Biphasic epithelial malignancy. Metastases may be uniphasic or mixed.
Carcinoma with pseudosarcomatous stroma	Uniphasic epithelial malignancy with a benign, atypical stromal reaction. Metastases are epithelial only.
Carcinoma and prior irradiation	Epithelial malignancy with post-irradiation stromal and epithelial atypia. Metastases are epithelial only.
Carcinosarcoma	True heterologous malignancy. Metastases may be mixed or uniphasic.
Pseudosarcomatous stromal reaction without coexisting carcinoma (historically or direct evidence)	Benign, atypical stromal reaction to injury (irradiation or unknown agents). Self-limited and local.

Conclusions on Sarcomatoid Carcinomas. For the present any conclusions about these unusual neoplasms cannot be finite. Debate over their cellular composition aside, however, it is clear that sarcomatoid carcinomas, as a group, manifest a biologic behavior that is more aggressive than most conventional squamous cell carcinomas. This is particularly true for sinonasal and supraglottic primaries. Patients with localized tumors in the glottis appear to fare better. Except for the possibility that polypoid tumors of the true vocal cords have a better short-term prognosis, there is no single accepted histopathologic or clinical finding of the primary that can portend a favorable response to treatment. A history of prior irradiation to the area of involvement may be a significant detriment. Depth of invasion by the sarcomatoid element may be related to prognosis. Consistent TNM classification of the lesions needs to be done before denying the importance of size and site.

Diagnosis and management of the patient is based on the collective experience of the whole group. Until definitive characterization of individual tumors can be made, there is a risk that some patients may be overtreated and that others will receive less than optimal treatment.

Perhaps a classification of the pseudosarcomatous lesions can provide a beginning (Table 4). The first four entries in the table require identification of an epithelial malignancy in the tumors. Carcinosarcomas are always controversial lesions; rare in the upper airway and oral cavity; and their distinction from sarcomatoid carcinomas, so far as treatment is concerned, is probably academic. A pseudosarcomatous reaction to known or unknown injury without an association with carcinoma, while fairly common in the superficial soft tissues of the head and neck, is unusual in the upper aerodigestive tracts (Fig. 11). Care must be exercised not to yield to the temptation to call such lesions malignant. Radiation injury to mucosal and subepithelial tissues can produce histologically abnormal epithelial and stromal cells. Indeed, prior irradiation compounds the surgical pathologic difficulties. The likelihood of radiation being a major etiologic factor in sarcomatoid carcinomas is, however, not great. In 118 cases in which information was available, only 26 of the patients (22%) had received antecedent irradiation, of varying doses and variable latent periods.[3,6,7,9,18,24]

NODULAR FASCIITIS

Nodular fasciitis, a benign pseudosarcomatous proliferative lesion of soft tissues and nearly always having a relationship to fascia or tendonous connective tissue, has some clinical and light-optic features of a sarcomatoid carcinoma. It is not a very commonly encountered lesion and Meister et al.[25] contend it is reasonable to assume an overall incidence of nodular fasciitis in an unselected biopsy material to be about 0.025%. The extramucosal soft tissues of the head and neck account for somewhat over 15% of the lesions (Table 5).[26-29]

Involvement of the mucosal surfaces of the head and neck is rarely reported but the true incidence is not possible to relate. Allen[27] records only 3 examples in 161 lesions (2 buccal and 1 esophageal) of the head and neck. Werning,[30] who restricted his study to nodular fasciitis of the orofacial region, described 5 cases in the oral mucosa (3 buccal, 1 lingual, and 1 in the mental foramen area). Emphasizing the origin from fascia and related structures, the parotid region (parotid sheath) is an area of relative predilection. Nine of 41 orofacial tumors described by Werning arose here, as did two of 18 tumors reported by Dahl and Jarlstedt.[31]

In the mucosa, nodular fasciitis has essentially the same clinical and biologic features as it does when located in preferred somatic soft tissue sites: rapid onset, nodular growth pattern, and a peak incidence between 30 and 40 years of age.[30,32] Approximately 7 to 12% of the lesions occur in children.[31] An unusual variant, termed intravascular fasciitis, also has a moderate predi-

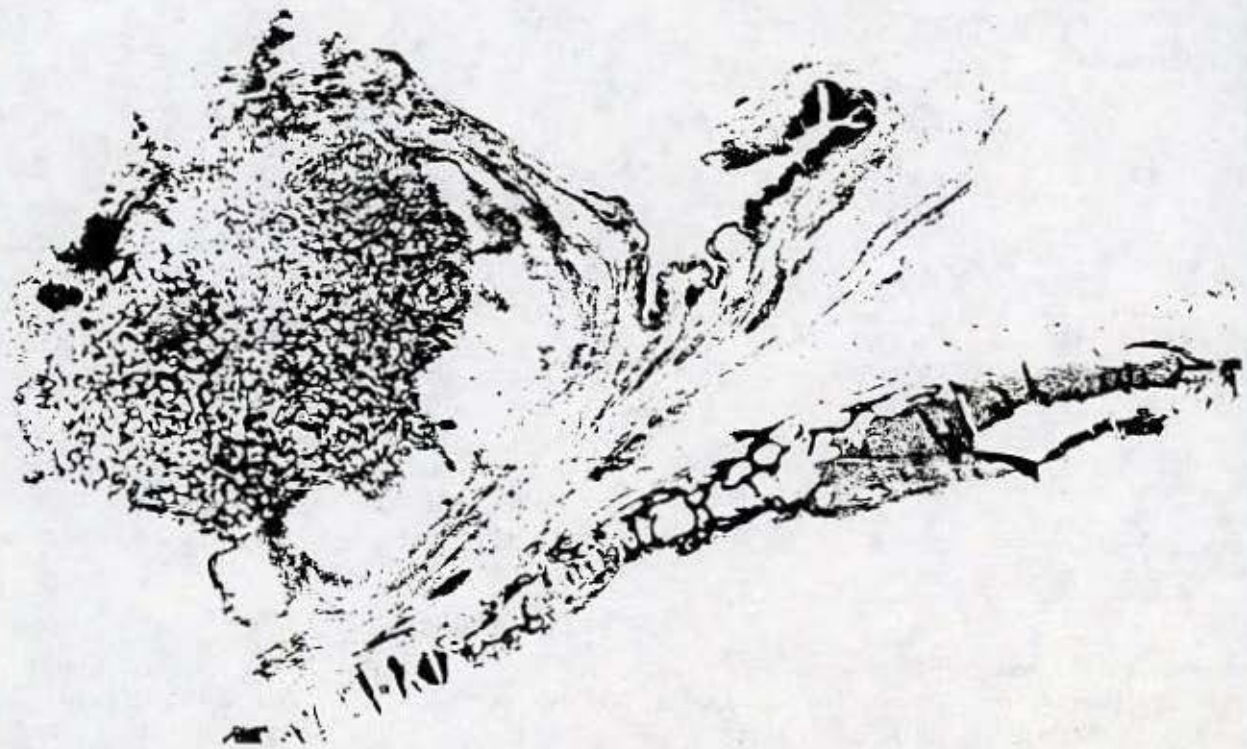

Figure 11 Non-neoplastic osteocartilaginous metaplasia of the vocal cord. Such extensive metaplasia is rare but should not be confused with sarcomatoid carcinoma. Hematoxylin and eosin ×10.

lection for the head and neck.[33] This lesion has the histologic features of a nodular fasciitis but with intraluminal, intramural, and extramural involvement of small to medium-sized arteries and veins. It occurs as a multinodular or serpentine growth along the affected blood vessels.

Histologically, nodular fasciitis presents a characteristic and striking appearance. If there is a single basic criterion for diagnosis, it may be the haphazard arrangement of irregular bundles or single fibroblastic cells in a mucoid matrix, but this does not suffice for diagnosis. An important and constant feature is the vasculature of the lesion, which is composed of a fine capillary network arranged in a radial pattern and apparently deriving its branching from larger vessels of adjacent tissues. Mitoses may be common and variable quantities of stromal products are seen, such as collagen fibers and acid mucopolysaccharides. Foamy histiocytes and absorptive-type giant cells can be found.

Table 5. Anatomic distribution of nodular fasciitis *

Anatomic site	No. of cases	Percent
Upper extremity	510	48
Trunk	215	20.3
Lower extremity	157	14.8
Head and neck	179	16.9
Total	1,061	100

*Compiled from data by Stout,[26] Allen,[27] Soule,[28] and Hutter et al.[29]

Ultrastructural and histo- and immunochemical procedures have demonstrated the principal cell in these lesions to be the myofibroblast.[34,35]

Myofibroblast. The myofibroblast is a unique stromal cell with contractile properties. It is now considered a fundamental, if not pivotal cell, in granulation tissue of healing wounds.[35] The cells appear in the stroma at the onset of wound contraction, increase in number during the period of maximal contraction, and decrease as wound contraction abates. The presence of the cell is not limited to granulation tissue and it seems as if its ubiquity rivals that of the lymphocyte and facultative "histiocytes."

The myofibroblast is best characterized as a cell form intermediate between fibroblasts and smooth muscle cells. Indeed, transitional stages have been described.[35] Origin of the cell is presumed to be from the fibroblasts, the smooth muscle cells, primordial mesenchymal cells, or all three.

Seemayer et al.[35] indicate the myofibroblast is

Table 6. Site distribution of 1,619 soft tissue sarcomas*

Site	Percent of total cases
Head and neck	12
Trunk	30
Upper extremity	16
Lower extremity	42

*From data provided by Rosenberg and Glatstein [36]

a principal cell in at least three basic pathologic settings: response to injury and repair, quasi-neoplastic proliferative conditions, and in the stroma of malignant neoplasms. All three are pertinent to the preceding discussion on sarcomatoid carcinomas. There is, however, little to support myofibroblastic participation in these lesions. Besides nodular fasciitis, the cells are found in desmoids, fibromatoses, angiofibromas, and in several forms of soft tissue sarcomas.[35] They also constitute part of a stromal response in carcinomas, especially in neoplasms with desmoplasia and retraction.[35] In comparison, noninvasive (intraepithelial) carcinomas and normal tissues lack stromal myofibroblasts. This suggests myofibroblasts may constitute a unique expression of host response to neoplasia. Also, low grade sarcomas that pursue a less aggressive biologic course tend to contain not only more but better formed myofibroblasts than high grade sarcomas.[35]

Myofibroblastic participation in some sarcomatoid carcinomas is suggested by the light-optic appearance of some of the spindle cells. This has never been confirmed. Since it is deemed a mesenchymally derived cell, only those putative sarcomatoid carcinomas without coexistent carcinoma should contain them in any number. Certainly its role as a host-defense mechanism is not very effective if it is a principal cell in sarcomatoid carcinomas. Finally, while it is possible the myofibroblast has neoplastic potential, no such lesion has been definitely reported.[35]

FIBROSARCOMA

Considering all forms and all age groups, the anatomic region of the head and neck is the least common site of origin of malignancies of soft-part tissues. Approximately 12 to 15% of soft tissue sarcomas arise there (Tables 6 and 7).[36,37] Table 7, derived from data presented by a task force for the development of a staging system of sarcomas, classifies the types of sarcomas (excluding leiomyosarcomas of the gastrointestinal tract) and also segregates those occurring in the head and neck.[37] These data are to be compared with those of Farr[38] (Table 8) which are limited to head and neck sarcomas. The relative frequency of fibrosarcoma in both series is remarkably close.

In former times, before refinements in diagnosis and classification, fibrosarcoma was a much more prevalent diagnosis. It is less so now, having been replaced by more precise histogenic and/or histopathologic diagnoses such as histiocytoma, neurogenous sarcoma, and synovial sarcoma. The present day diagnosis of fibrosarcoma is made only when other tumors which may demonstrate fibrous tissue and collagen production are excluded.

The tabular data on incidence of fibrosarcomas refer to fibrosarcomas in aggregate and almost exclusively to extramucosal-extravisceral sites. Those tumors presumed to arise from the soft tissues of the upper aerodigestive tracts are even less frequent. Fu and Perzin[39] have reported 13 fibrosarcomas of the nasal cavity, paranasal sinuses, and nasopharynx and accepted seven more from the preceding, recent literature. To these cases can be added the seven reported by Swain and associates.[40] Even from this small number, it is evident that (*1*) any sinus may be involved, (*2*) the maxillary antrum is a site of predilection, (*3*) confinement of the neoplasm to a single sinus or the nasal cavity at the time of diagnosis is not the norm.

Approximately 35 cases of laryngeal fibrosarcoma have been reported.[41] The exact site of origin is often obscured by the neoplastic bulk but most of the tumors are thought to arise from the anterior part of the true cords, the anterior commissure, or both; others arise at the level of the ventricle or cricoid cartilage.

Fibrosarcomas, not otherwise classified as fibromatoses or neurofibrosarcomas, are surprisingly uncommon in the oral cavity and the paraoral soft tissues. Furthermore, even though their number is small, the majority of oral fibrosarcomas are not of soft-tissue origin, but are periosteal fibrosarcomas. It is also quite likely that most fibrosarcomas of the paranasal sinuses originate in the periosteum of the bony walls of the sinuses.

Fibrosarcomas can occur at any age. There is a small yet definite peak at birth or during the first years of life, when distinction from fibromatosis is difficult. With such separation, however, fibrosarcoma ranks second only to rhabdomyosarcoma as the most common soft tissue sarcoma in the pediatric age group (Table 9).[42] About 16% of the sarcomas in these patients afflict the head and

Table 7. Percent incidence by histologic type of soft tissue sarcoma in the head and neck *

Sarcoma	No. of cases (%)	No. of cases in head and neck	Percent of specific sarcoma in head and neck
Rhabdomyosarcoma	234 (19.3)	80	34.2
Fibrosarcoma	231 (19.0)	37	16.0
Liposarcoma	221 (18.2)	10	4.5
Malignant fibrous histiocytoma	128 (10.5)	9	7.0
Synovial sarcoma	84 (6.9)	1	1.2
Leiomyosarcoma	79 (6.5)	2	2.5
Neurogenous sarcoma	60 (4.9)	15	25
Angiosarcoma	33 (2.7)	5	15
Unclassified and miscellaneous	145 (12.0)	18	12.4
Total	1,215 (100)	177	

*Extracted and compiled from data presented by Russell et al [41]

neck.[43,44] Sixty percent of all fibrosarcomas, regardless of site, however, occur in patients who are between 40 and 70 years of life and this holds true for lesions in the upper airway.

Fibrosarcomas of the nasal cavity, paranasal sinuses, and larynx typically grow as polypoid masses with sizes ranging from 2 to 8 cm. The tumors may appear circumscribed but are not encapsulated. Adjacent bone can be destroyed either by direct invasion or by expansion atrophy. Their infiltrative margins are usually blunt.

The histopathology of the sarcomas is that of a spindle cell tumor with a pattern of interlacing fascicles (herringbone pattern). Marked pleomorphism is not a feature (Fig. 12). Mitoses are always found and are sometimes numerous. Histologic grading of fibrosarcomas should always be done since grade relates to recurrences and survival figures.[45,46] The 3 or 4 histologic grades are based on the degree of cellularity and anaplasia of the neoplastic cells, the relative amount of collagen and reticulin produced, and frequency of mitoses (Fig. 13). Degree of local infiltration is also assumed. A low-grade, or well-differentiated, fibrosarcoma manifests abundant reticulin, a low degree of cellularity, little anaplasia, and a low mitotic count. High-grade fibrosarcomas have clinically or microscopically occult ramifications and/or skip areas, in turn promoting recurrences contiguous with, but at a distance from, the primary mass.

Soft tissue tumors called fibrosarcomas occurring during the first 3 to 5 years of life appear to exhibit a biologic behavior considerably better than those occurring in later life.[43,44,46] The majority of the lesions are present at birth or are noticed within the first few months of life. The head and neck, and especially the airway, is not a region of predilection. Most are seen in the extremities (foot and ankle, forearm, and lower leg).

The tumors manifest progressive enlargement with some attaining considerable size before

Table 8. Incidence of specific sarcomas as judged by admission to a cancer head and neck service.*

Class of sarcoma	No. of cases	Percent
Rhabdomyosarcoma	96	48.5
Fibrosarcoma	34	17.2
Neurogenous sarcoma	22	11.1
Angiosarcoma	19	9.6
"Undifferentiated" spindle cell sarcoma	14	7.1
Liposarcoma	5	2.5
Synovial sarcoma	4	2.0
Leiomyosarcoma	4	2.0
Total	198	100

*Compiled from data presented by Farr [38]

Table 9. Incidence of soft tissue sarcomas in children.*

Type of sarcoma	Incidence/10^6 children	Percent of all cases
Rhabdomyosarcoma	4.00	51.4
Fibrosarcoma	0.84	10.8
Synovial sarcoma	0.44	5.6
Liposarcoma	0.35	4.5
Neurofibrosarcoma	0.26	3.4
Sarcoma, not specified	0.82	10.6
Other	1.00	13.5
Total	7.71	100

*Modified from King and Clatworthy [42]

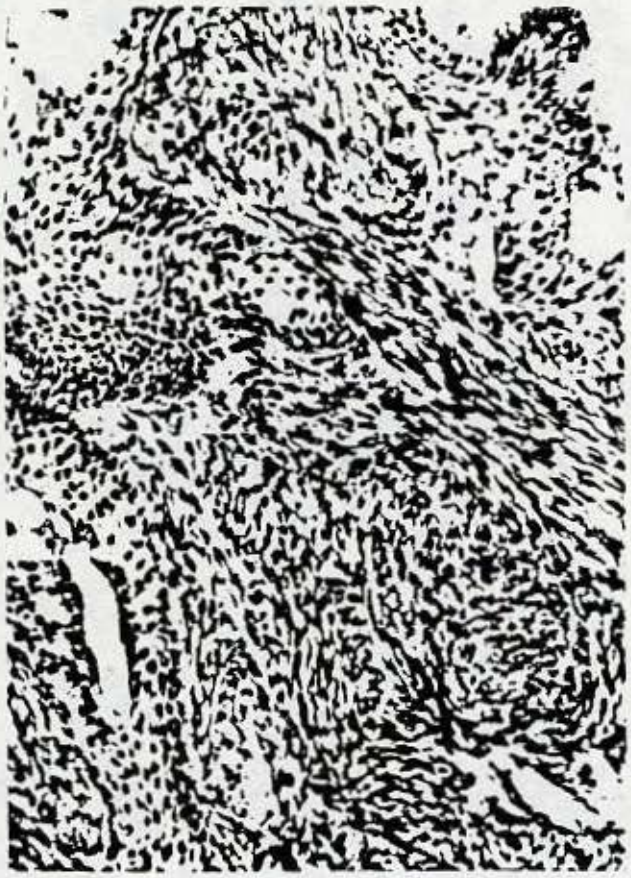

Figure 12. Low-grade fibrosarcoma of the paranasal sinuses. The patient, a man of 57 years, has had recurrent neoplasm necessitating six surgical excisions over an 18-year period. Hematoxylin and eosin ×170.

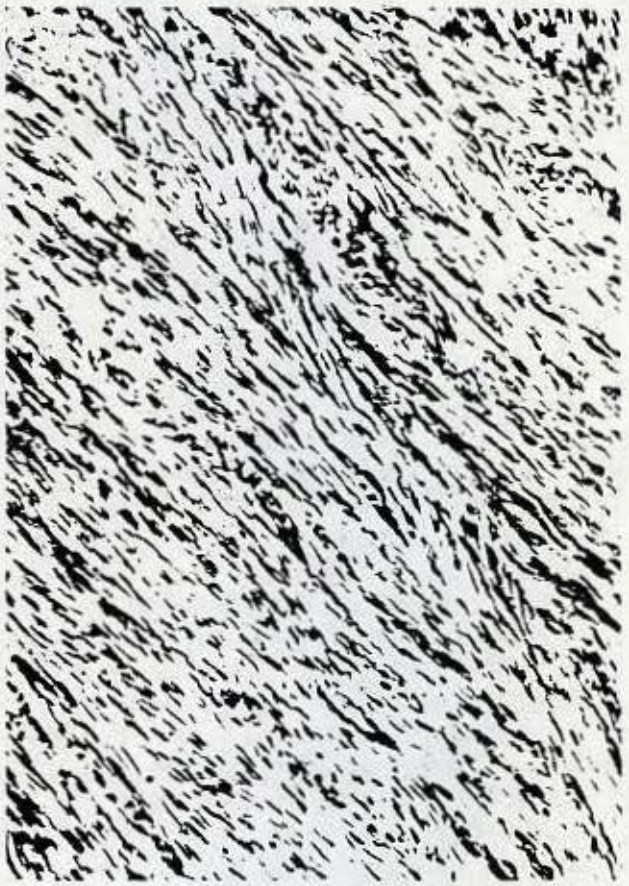

Figure 13. Low-grade fibrosarcoma of the larynx. The neoplasm, although moderately cellular, contains few mitoses and a moderate amount of collagen. Hematoxylin and eosin ×180.

diagnosis. For the most part, these fibrosarcomas are much less differentiated than fibrosarcomas in adults. Mitoses are common.

Despite the mitotic activity and a lesser degree of differentiation, recurrences and metastases are fewer than for the tumors in adults. Even within the childhood-adolescent period, however, there are demonstrable differences in biologic behavior. Soule and Pritchard,[44] in their study of 110 patients under the age of 15 years, found a local recurrence rate of 43% and a metastatic rate of 7.3% for neoplasms occurring within the first 5 years. After the age of 10 years, both rates approached those of adults, e.g., a metastatic rate of more than 50%.

For fibrosarcomas in adults at all sites, local recurrences have varied from 56% to 75%. Metastases appear related to a lack of local control. In one study, there was a 59% rate of metastasis in those tumors with recurrences as compared with only 22% in those without recurrence.[47] Metastases, in children or adults, may often be delayed, possibly 5 or 10 years or longer from the time of primary treatment. Survival also correlates with absence of local control of disease and metastases; it is reduced by half (65% vs 30%) at 10 years.[45]

Besides the influence of the age of the patient on the biologic course of a fibrosarcoma, histopathologic differentiation of the tumors, anatomic site of origin, and mode of therapy play modifying roles. Table 10 portrays the effect of histologic grade on survival for fibrosarcomas in general.[46] Well-differentiated fibrosarcomas usually do not metastasize but have a respectable re-

Table 10. Influence of histologic grade of fibrosarcoma on survival.*

Grade	10-yr survival (%)
4	0
3	27
2	37
1	80

*Modified from Enterline.[46]

currence rate of about 40%. Poorly differentiated fibrosarcomas nearly double the recurrence rate and about 25% manifest metastases.[41]

Sinonasal mucosal fibrosarcomas exhibit similar characteristics except that a strong correlation with histologic grade has not been established.[39] Metastases, lymphatic or hematogenous, are also unusual. Death in these patients is attributable to local tumor growth, such as direct intracranial invasion or massive local recurrence. In these instances, recurrences and/or persistence of disease have followed limited local resections. Fu and Perzin[39] indicate that if no neoplastic tissue is present at the surgical margins, the prognosis appears to be relatively good compared with other sarcomas involving this area. Our personal experience coincides. We further have noted that fibrosarcomas of this anatomic region are usually lower grade tumors except for those arising in patients who had received prior irradiation for other lesions.

The behavior of fibrosarcomas of the larynx is significantly modified by histologic grade and by size of the tumors.[48] High-grade, large tumors behave much like their somatic counterparts except that lymph node metastases are unusual.

Enucleation or simple excision of any soft tissue sarcoma almost always is followed by local recurrence and fibrosarcomas are no exceptions. Several features intrinsic to their growth pattern are responsible. Many of the tumors appear to be enveloped by a pseudocapsular membrane that belies the infiltrative character of the lesion. The neoplasms penetrate this membrane with finger-like extensions beyond the gross capsule. Other sarcomas are so poorly defined that clinical or even intraoperative palpation cannot define their extent.

The high recurrence rates of even low-grade fibrosarcomas, the morbidity of local infiltration, and mortality of these tumors indicate wide-field surgical excision is the primary form of treatment. At any site, late recurrent or metastatic lesions are encountered, indicating that long-term follow-up is necessary before an assumption of "cure."

Even with the advances in radiotherapy over the past two decades, it is not likely this modality will supercede surgical excision for fibrosarcomas.[36,49] It does appear, however, that radiation therapy given as a postoperative adjuvant to surgery may be useful in reducing local recurrence rates.[36,49] To date, this premise almost exclusively relates to sarcomas of the extremities and even for these lesions, the long-term effectiveness of radiation therapy in sterilizing microscopic disease is unclear.[36]

SUMMARY

The pathology of three spindle cell lesions—sarcomatoid carcinomas, nodular fasciitis, and fibrosarcoma—involving the mucosae of the upper airway and oral cavity has been presented. Although sharing some histopathologic features, each of these tumors has a different histogenesis and biologic course. Sarcomatoid carcinomas, as defined by the authors, are epithelial malignancies (almost always epidermoid) in which a pseudosarcomatous component dominates their microscopic appearance. In aggregate, sarcomatoid carcinomas exhibit a biologic aggressiveness greater than non-sarcomatoid carcinomas. Fibrosarcomas are unusual supporting tissue neoplasms in the airway and especially in the oral cavity. They are fibroblastic tumors in which their behavior is modified by age of the patient, site of the lesion, and histologic grade and size of the neoplasm. Nodular fasciitis is a pseudosarcomatous, benign and non-neoplastic reactive lesion that is unusual in the mucous membranes. The next part in this series will consider variable neoplastic expressions of the squamous cell in the head and neck.

REFERENCES

1. Batsakis JG: "Pseudosarcoma" of the mucous membranes in the head and neck. *J Laryngol Otol* 95:311–316, 1981.
2. Hyams VJ: Spindle cell carcinoma of the larynx. *Canad J Otolaryngol* 4:307–313, 1975.
3. Ellis GL, Corio RL: Spindle cell carcinoma of the oral cavity. A clinicopathologic assessment of fifty-nine cases. *Oral Surg* 50:523–534, 1980.
4. Friedel W, Chambers RG, Atkins JP, Jr: Pseudosarcomas of the pharynx and larynx. *Arch Otolaryngol* 102:286–290, 1976.
5. Howell JH, Hyams VJ, Sprinkle PM: Spindle cell carcinoma of the nose and paranasal sinuses. *Surg Forum* 29:565–568, 1978.
6. Randall G, Alonso WA, Ogura JH: Spindle cell carcinoma (pseudosarcoma) of the larynx. *Arch Otolaryngol* 101:63–66, 1975.
7. Goellner JR, Devine KD, Weiland LH: Pseudosarcoma of the larynx. *Am J Clin Pathol* 59:312–326, 1973.
8. Lane N: Pseudosarcoma (polypoid sarcoma-like masses) associated with squamous-cell carcinoma of the mouth, fauces, and larynx. Report of ten cases. *Cancer* 10:19–56, 1957.
9. Leventon GS, Evans HL: Sarcomatoid squamous cell car-

cinoma of the mucous membranes of the head and neck: A clinicopathologic study of 20 cases. *Cancer* 48:994–1003, 1981.
10. Lichtiger B, Mackay B, Tessmer CF: Spindle-cell variant of squamous carcinoma: A light and electron microscopic study of 13 cases. *Cancer* 26:1311–1320, 1970.
11. Kleinsasser O, Glanz H: Sarkomähnliche Gewebsbilder in Larynxkarzinomen (Pseudosarkome, Karzinosarkome, Spindelzellkarzinome, pleomorphe Karzinome). *Laryngol Rhinol Otol* (Stuttg) 57:225–234, 1978.
12. Harris M: Differential diagnosis of spindle cell tumours by electron microscopy—personal experience and a review. *Histopathology* 5:81–105, 1981.
13. Battifora H: Spindle cell carcinoma. Ultrastructural evidence of squamous origin and collagen production by the tumor cells. *Cancer* 37:2275–2282, 1976.
14. Matsusaka T, Watanabe H, Enjoji M: Pseudosarcoma and carcinosarcoma of the esophagus. *Cancer* 37:1546–1555, 1976.
15. Feldman PS, Barr RJ: Ultrastructure of spindle cell squamous carcinoma. *J Cutan Pathol* 3:17–24, 1976.
16. Someren A, Karcioglu Z, Clairmont AA: Polypoid spindle-cell carcinoma (pleomorphic carcinoma). Report of a case occurring on tongue on review of the literature. *Oral Surg* 42:474–489, 1976.
17. Ferlito A: Histocytic tumors of the larynx. A clinicopathologic study and review of the literature. *Cancer* 42:611–622, 1978.
18. Appleman HD, Oberman HA: Squamous cell carcinoma of the larynx with sarcoma-like stroma. *Am J Clin Pathol* 44:135–145, 1965.
19. Himalstein MR, Humphrey TR: Pleomorphic carcinoma of the larynx. *Arch Otolaryngol* 87:389–395, 1968.
20. Sherwin RP, Strong MS, Vaughn CW, Jr.: Polypoid and junctional squamous cell carcinoma of the tongue and larynx with spindle cell carcinoma ("pseudosarcoma"). *Cancer* 16:51–60, 1963.
21. Grigg JW, Rachmaninoff N, Robb JM: Pseudosarcoma associated with squamous cell carcinoma of the larynx. Report of a case. *Laryngoscope* 71:555–561, 1961.
22. Evans, HL, Smith JL: Spindle cell squamous carcinomas and sarcoma-like tumors of the skin. A comparative study of 38 cases. *Cancer* 45:2687–2697, 1980.
23. Osamura RY, Shimamura K, Hata J, Tamaoki N, Watanabe K, Kubota M, Yamazaki S, Mitomi T: Polypoid carcinoma of the esophagus. A unifying term for "carcinosarcoma" and "pseudosarcoma." *Am J Surg Pathol* 2:201–208, 1978.
24. Lambert PR, Ward PH, Berri G: Pseudosarcoma of the larynx. A comprehensive analysis. *Arch Otolaryngol* 106:700–708, 1980.
25. Meister P, Buckmann FW, Konrad E: Nodular fasciitis (analysis of 100 cases and review of the literature). *Path Res Pract* 162:133–165, 1978.
26. Stout AP: Pseudosarcomatous fasciitis in children. *Cancer* 14:1216–1222, 1961.
27. Allen PW: Nodular fasciitis. *Pathology* 4:9–26, 1972.
28. Soule EH: Proliferative (nodular) fasciitis. *Arch Pathol* 73:437–444, 1962.
29. Hutter RVP, Stewart FW, Foote FW Jr.: Fasciitis. A report of 70 cases with follow-up proving the benignity of the lesion. *Cancer* 15:992–1003, 1962.
30. Werning JT: Nodular fasciitis of the orofacial region. *Oral Surg* 48:441–446, 1979.
31. Dahl I, Jarlstedt J: Nodular fasciitis in the head and neck. A clinicopathological study of 18 cases. *Acta Otolaryngol* 90:152–159, 1980.
32. Larsson A, Svartz K: Nodular fasciitis in the oral cavity. *Int J Oral Surg* 5:122–127, 1976.
33. Patchefsky AS, Enzinger FM: Intravascular fasciitis. A report of 17 cases. *Am J Surg Pathol* 5:29–36, 1981.
34. Wirman JA: Nodular fasciitis, a lesion of myofibroblasts. An ultrastructural study. *Cancer* 38:2378–2389, 1976.
35. Seemayer TA, Schurch W, Legace R: Myofibroblasts in human pathology. *Hum Pathol* 12:491–492, 1981.
36. Rosenberg SA, Glatstein EJ: Perspectives on the role of surgery and radiation therapy in the treatment of soft tissue sarcomas of the extremities. *Semin Oncol* 8:190–200, 1981.
37. Russell WO, Cohen J, Enzinger F, Hajdu SI, Heise H, Martin RG, Meissner W, Miller WT, Schmitz RL, Suit HD: A clinical and pathological staging system for soft tissue sarcomas. *Cancer* 40:1562–1570, 1977.
38. Farr HW: Soft part sarcomas of the head and neck. *Semin Oncol* 8:185–189, 1981.
39. Fu Y-S, Perzin KH: Nonepithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx. A clinicopathologic study. VI. Fibrous tissue tumors (fibroma, fibromatosis, fibrosarcoma). *Cancer* 37:2912–2928, 1976.
40. Swain RE, Sessions DG, Ogura JH: Fibrosarcoma of the head and neck: A clinical analysis of forty cases. *Ann Otol Rhinol Laryngol* 83:439–444, 1974.
41. Gorenstein A, Neel HB, III, Weiland LH, Devine KD: Sarcomas of the larynx. *Arch Otolaryngol* 106:8–12, 1980.
42. King DR, Clatworthy W: The pediatric patient with sarcoma. *Semin Oncol* 8:215–221, 1981.
43. Chung EB, Enzinger FM: Infantile fibrosarcoma. *Cancer* 38:729–739, 1976.
44. Soule EH, Pritchard DJ: Fibrosarcoma in infants and children. A review of 110 cases. *Cancer* 40:1711–1721, 1977.
45. Pritchard DJ, Soule EH, Taylor WF, Ivins JC: Fibrosarcoma—a clinicopathologic and statistical study of 199 tumors of the soft tissues of extremity and trunk. *Cancer* 33:888–897, 1974.
46. Enterline HT: Histopathology of sarcomas. *Semin Oncol* 8:133–155, 1981.
47. Van der Werf-Messing B, Van Unnik JAM: Fibrosarcoma of the soft tissues—a clinicopathologic study. *Cancer* 18:1113–1123, 1965.
48. Batsakis, JG, Fox JE: Supporting tissue neoplasms of the larynx. *Surg Gynecol Obstet* 131:989–997, 1970.
49. Lindberg RD, Martin RG, Romsdahl MM, Barkley HT: Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. *Cancer* 47:2391–2397, 1981.

Case 24. Submandibular gland, carcinoma ex pleomorphic adenoma

There is histologic evidence of malignancy in this pleomorphic adenoma. It is manifested by destructive infiltrative growth at the periphery and by dysplastic ducts in areas of the pleomorphic adenoma. It is a carcinoma ex pleomorphic adenoma. For that diagnosis, one must have either histologic evidence of a maternal pleomorphic adenoma or historical evidence of it.

Within the group of carcinomas ex pleomorphic adenoma, the prognosis is largely dependent on size of the carcinomas and also on the histologic subtype of the carcinoma (see accompanying reprint). A so-called carcinoma in-situ exists (carcinoma confined to the pleomorphic adenoma) and its behavior is that of the pleomorphic adenoma.

Biologic and chronologic time foster malignancy to develop in pleomorphic adenomas. It is therefore the responsibility of the first surgeon to extripate the original benign tumor as clearly and cleanly as possible.

Carcinomas Ex Pleomorphic Adenoma and Malignant Mixed Tumors

Histomorphologic Indexes

Maria E. Tortoledo, MD; Mario A. Luna, MD; John G. Batsakis, MD

• **Clinical and pathologic differences exist between the several neoplasms encompassed by the term *malignant mixed tumors* of salivary glands. The majority of the neoplasms are carcinomas ex pleomorphic adenoma. True malignant mixed tumors (carcinosarcomas) are rare, and even more rare are the benign metastasizing mixed tumors. This study of 40 *malignant mixed tumors* indicates that two previously unreported variables, measured invasion in millimeters and histologic subclassifications of the malignant neoplasm, are valuable guides to prognosis and biologic behavior. All patients whose malignant neoplasm extended for more than 8 mm beyond residual capsule or benign residual tumor died of their disease. The extent of invasion also correlated with perineurial invasion, involvement of bone, and metastases to lymph nodes. Histologic subclassification points out that there is no prototypical carcinoma ex pleomorphic adenoma and that high- and low-grade carcinomas can be found. Only one of the patients with low-grade (terminal duct) carcinomas died of his disease during follow-up periods extending to over 20 years.**

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For malignant neoplasms of salivary tissues, two of the better determinants of prognosis are histologic classification and size of the neoplasm.[1,2] These indexes, along with others, have been applied with varying degrees of success to nearly all malignant salivary gland neoplasms. The "malignant mixed tumor" poses special problems for the use of these variables. The first relates to the generic and inappropriate use of malignant mixed tumor as a specific histopathologic entity; the second is that gross size is not a measure of the malignant component in most malignant mixed tumors.

The great majority of so-called malignant mixed tumors of salivary tissues are carcinomas arising in or from a mixed tumor (pleomorphic adenoma).[3] Under the rubric *malignant mixed tumor*, however, there are other histologically definable neoplasms. Only the epithelial component is malignant in the carcinoma arising in a mixed tumor (carcinoma ex pleomorphic adenoma). The carcinoma may either be confined within the maternal mixed tumor or it may be invasive and capable of metastasizing. The other histologic variants are only rarely encountered. In one, the true malignant mixed tumor, there is a heterologous malignant neoplasm (carcinosarcoma), with malignant cartilage most often representing the nonepithelial component of the biphasic malignant neoplasm.[3] Metastases from the true malignant mixed tumor usually contain both tissue components; only carcinoma is found in the metastatic deposits from a carcinoma ex pleomorphic adenoma. The most unusual and rarest variant is the metastasizing mixed tumor, defined as a histologically benign tumor, that inexplicably manifests distant metastases.[3]

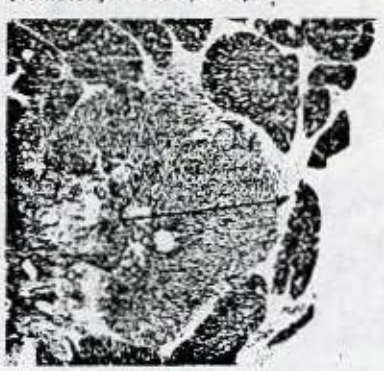
Reports of clinical series concerned with the management and prognosis of malignant mixed tumors have dealt almost exclusively with carcinomas ex pleomorphic adenoma, and in general these tumors have been regarded as high-grade salivary malignant neoplasms.[1,4,5]

The present study was undertaken in the belief that there exist biologic differences in the behavior of lesions currently generically grouped as malignant mixed tumors.

MATERIALS AND METHODS

Medical records and tissue sections of 74 patients coded as having malignant mixed tumors of the salivary glands and treated

Fig 1.—Carcinoma ex pleomorphic adenoma. Residual mixed tumor is within dotted lines, measured invasion along solid line (hematoxylin-eosin, ×10).



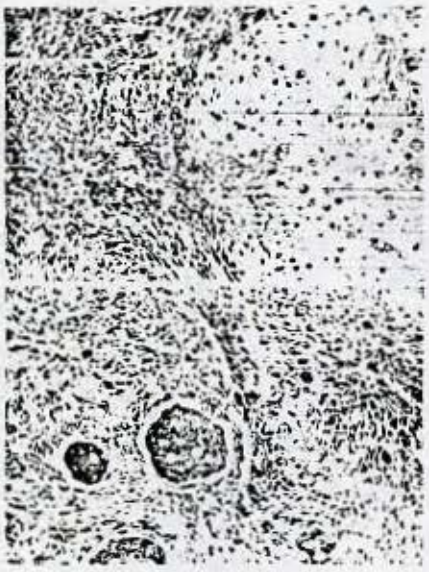


Fig 2.—True malignant mixed tumor (carcinosarcoma). Top, Chondrosarcoma component showing differentiated and dedifferentiated elements. Bottom, Ductal carcinoma within sarcomatous matrix (hematoxylin-eosin, ×85).

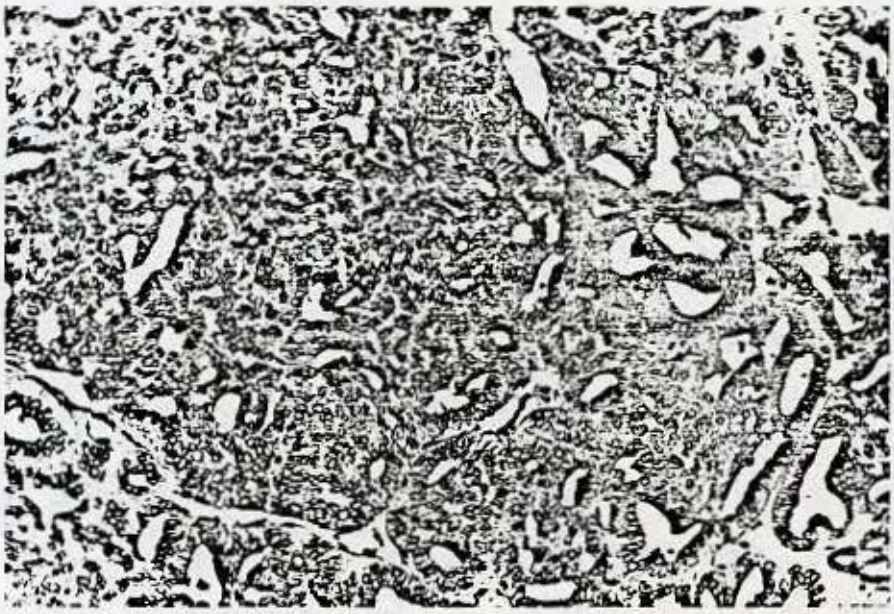


Fig 3.—Carcinoma ex pleomorphic adenoma, terminal duct type. This carcinoma is characterized by small ductal structures, often in association with solid epithelial areas. Nuclei are typically vesicular (hematoxylin-eosin, ×150).

at the University of Texas, M. D. Anderson Hospital and Tumor Institute at Houston between 1955 and 1975 were examined. Nineteen patients were excluded because (1) there was less than a five-year follow-up period or (2) histologic materials were not available for review. Another 15 patients were eliminated because the surgical-pathologic diagnosis could not be established with certainty. Forty patients remained as the definitive study group.

Histologic Examination

Inclusion of case material required the presence of histologic evidence of a benign mixed tumor in association with the malignant component. Hematoxylin-eosin-stained sections of primary and recurrent lesions were examined without foreknowledge of the patient's clinical course. An average of seven sections per case were evaluated and the following observations were recorded in each case: (1) histologic type of the malignant component, (2) regional structures invaded (nerve, bone, muscle), (3) metastases to regional lymph nodes, (4) status of surgical margins, and (5) objective measurement of histologic microinvasion.

Two methods were used to measure the extent of invasion by the malignant neoplasm arising in the mixed tumor, an ocular micrometer and a ×2.5 (magnification) objective in a standard light microscope and the 2.5-objective combined with a transparent millimeter ruler placed directly onto the hematoxylin-eosin-stained slide. The correlation between these two methods was excellent. All of the microscopic measurement data presented in this report were obtained by the transparent ruler method.

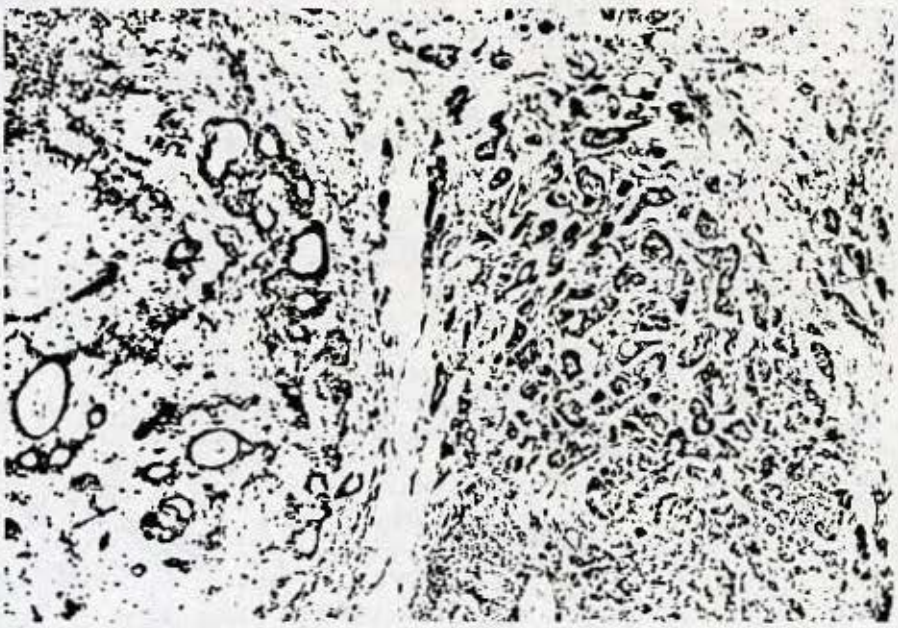


Fig 4.—Ductal carcinoma ex pleomorphic adenoma on right; residual benign pleomorphic adenoma on left (hematoxylin-eosin, ×60).

The following two microscopic landmarks were used for the placement of the zero marker of the ruler: (1) persistent capsule and/or stromal condensation about the mixed tumor and (2) identifiable residual benign mixed tumor, most often chondroid matrix. Actual measurements were made at right angles from the residual benign component nearest the capsule to the most distant infiltrative edge of the carcinoma (Fig 1). There were no intracapsular carcinomas in this series. An average of seven slides per case were studied and the quantitation recorded was the maximum measured in all slides.

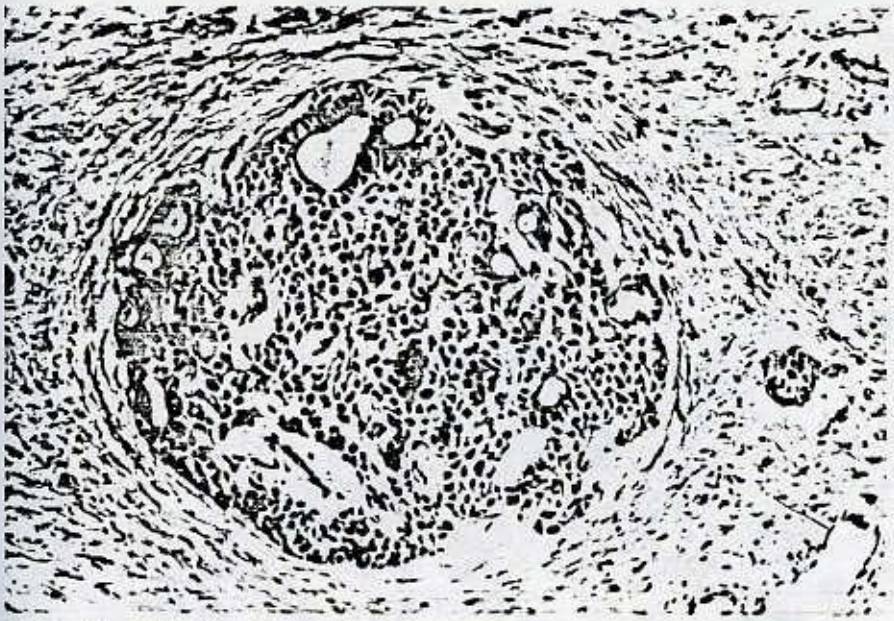


Fig 5.—Myoepithelial carcinoma arising in pleomorphic adenoma. This invasive neoplasm shows sparse duct formation. Preponderant cell is myoepithelial-like (hematoxylin-eosin, ×100).

Table 1.—Relationship of Invasion in Malignant Mixed Tumors to Survival*

Invasion, mm	No. of Cases	DOD	NED	DOC	LWD	LFU
1-8	17	0	7	8	1	1
9-12	5	5	...	...	...	...
13-16	9	9	...	...	...	...
17-20	3	2	...	...	...	1
Unable to establish	6	5	...	1	...	...
Total	**40**	**21**	**7**	**9**	**1**	**2**

*DOD indicates patients who died as a consequence of their neoplasms; NED, patients alive without evidence of neoplasm; DOC, patients who died of unrelated causes and were free of their cancer at the time of death; LWD, patients alive with evidence of neoplasm; and LFU, patients unavailable for follow-up after five years, but who had no clinical evidence of neoplasm at the last examination.

Table 2.—Surgical Margins and Follow-up Status

Status of Surgical Margins	No. of Patients	Local Recurrence	Regional Node Metastasis	Recurrence and Nodal Metastases	Follow-up Status*		
					DOD	NED	LWD
Positive	12	7	5	4	9	2	1
Negative	24	8	4	2	8	16	0

*DOD indicates patients who died as a consequence of their neoplasms; NED, patients alive without evidence of neoplasm; and LWD, patients alive with evidence of neoplasm.

Table 3.—Treatment of Malignant Mixed Tumors and Follow-up Status*

Treatment	No. of Patients	DOD	NED	DOC	LWD	LFU
Surgery	19	7	2	8	1	1
Radiation	2	2	...	...	...	...
Surgery and radiation	19	12	5	1	...	1
Total	**40**	**21**	**7**	**9**	**1**	**2**

*DOD indicates patients who died as a consequence of their neoplasms; NED, patients alive without evidence of neoplasm; DOC, patients who died of unrelated causes and were free of their cancer at the time of death; LWD, patients alive with evidence of neoplasm; and LFU, patients unavailable for follow-up after five years, but who had no clinical evidence of neoplasm at the last examination.

Clinical Chart Review

The following were extracted after review of the patient's clinical record: (1) sex and age of the patients, (2) location and gross size of the neoplasms, (3) determination of primary v recurrent neoplasms, (4) frequency of recurrences, and (5) follow-up status. For the latter, the following categories were established:

1. Patients who died as a consequence of their neoplasms
2. Patients alive without evidence of neoplasm
3. Patients who died of unrelated causes and were free of their cancer at the time of death
4. Patients alive with evidence of neoplasm
5. Patients unavailable for follow-up after five years, but who had no clinical evidence of neoplasm at the last examination

Survival times were measured from the date of the first histologic diagnosis of malignant neoplasm to the time of death or to the last follow-up visit. Unless the patient died of the cancer, the minimum accepted follow-up period was five years.

RESULTS

The age of the patients at the time of histologic diagnosis ranged from 24 to 68 years (mean, 58.3 years). There were 18 men and 22 women. Twenty-nine of the neoplasms were in major salivary glands and 11 arose in minor salivary tissue. The anatomic distribution of the neoplasms was as follows: parotid glands, 26; submandibular gland, three; palate, seven; other intraoral sites, three; and nasal cavity, one.

Thirty-seven of the malignant neoplasms were carcinomas ex pleomorphic adenoma; three were true malignant mixed tumors (carcinosarcomas). Five of the carcinomas were recurrent when first treated at M. D. Anderson Hospital. Histopathologic subclassification of the carcinomas yielded 13 ductal, ten undifferentiated, nine terminal duct, and three myoepithelial types. Two of the carcinomas could not be subclassified because of the small size of the surgical specimens.

Sarcoma was the preponderant component in the true malignant mixed tumors. In each, the sarcoma was a chondrosarcoma (Fig 2). The carcinomas designated terminal duct carcinomas were readily separated

from those called ductal carcinomas ex pleomorphic adenoma.[6,7] Terminal duct carcinomas were composed of rather uniform small cells arranged either in solid epithelial masses or as small tubuloductular elements (Fig 3). The neoplastic ducts in ductal carcinomas were larger, more pleomorphic, and often manifested an eosinophilic cytoplasm (Fig 4). Terminal duct carcinomas resembled the embryonic salivary duct anlage, while ductal carcinomas resembled infiltrative ductal carcinomas of the breast. Undifferentiated carcinomas exhibited no differentiation and were composed of anaplastic round cells of varying sizes and shapes. *Myoepithelial carcinoma* is the term we have tentatively applied to three of the malignant neoplasms because of their light-optic similarity to putative myoepithelial cells in benign mixed tumors, ie, plasmacytoid, myofibroblastlike, and clear cell areas. Definable ducts were sparse in these tumors and all demonstrated infiltrative growth (Fig 5).

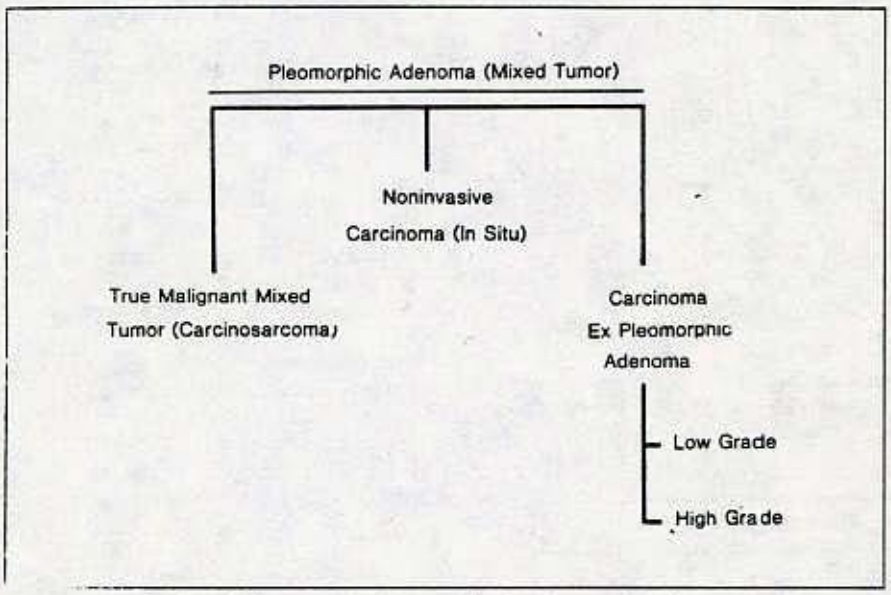


Fig 6.—Malignant neoplasms arising in pleomorphic adenoma.

Table 4.—Histologic Classification of Malignant Neoplasms in Mixed Tumor and Follow-up Status*

Histologic Classification	No. of Cases	DOD	NED	DOC	LWD	LFU
Ductal carcinoma	13	6	3	2	1	1
Undifferentiated carcinoma	10	7	...	2	...	1
Terminal duct carcinoma	9	1	4	4	...	...
Myoepithelial carcinoma	3	2	...	1	...	...
True malignant mixed	3	3	...	...	...	...
Unclassified	2	2	...	...	...	...
Total	40	21	7	9	1	2

*DOD indicates patients who died as a consequence of their neoplasms; NED, patients alive without evidence of neoplasm; DOC, patients who died of unrelated causes and were free of their cancer at the time of death; LWD, patients alive with evidence of neoplasm; and LFU, patients unavailable for follow-up after five years, but who had no clinical evidence of neoplasm at the last examination.

Table 5.—Incidence of Malignant Mixed Tumors and Carcinosarcomas*

Anatomic Site	Total Malignant Neoplasms	No. (%) of Malignant Mixed Tumors	No. (%) of Carcinosarcomas
Major salivary glands	895	72 (8)	2 (0.2)
Nasal cavity, sinuses, ears	603	1 (0.16)	0
Oral cavity and lips	6,786	12 (0.17)	0
Oral cavity and lips, salivary sites only	277	12 (4.3)	0

*These are microscopically confirmed cases, 1973 through 1977, US (excluding Puerto Rico) cancer incidence data. Data from *Surveillance, Epidemiology, End Results.*

Twenty-one patients died of causes related to their neoplasms. The time intervals between histopathologic diagnosis and death ranged from one month to 17 years (mean, four years). Only four of the dead patients survived longer than five years. Death in 19 patients was associated with distant metastases (principally to lungs and bones). Eleven of the 19 patients had concurrent local disease. Extensive local recurrence was responsible for the death of two patients.

The follow-up intervals for the remaining 19 patients ranged from five to 25 years (mean, 10.5 years), with ten patients having been seen last between five and eight years after treatment.

Table 1 presents the correlation between measured invasion (millimeters) and follow-up status. None of the patients in this series died of their disease when the microscopic invasion was less than 8 mm. All patients (17 of 17) whose malignant neoplasms extended for more than 8 mm died as a consequence. Only one of the nine histologically low-grade (terminal duct) carcinomas manifested invasion of more than 8 mm.

A similar, albeit less striking, relationship also existed between invasion and recurrences and metastases to regional lymph nodes. When the microscopic invasion exceeded 6 mm, the local recurrence rate was 70.5%. Neoplasms with less than 6 mm of invasion manifested a 16.5% rate of recurrence. Only two of 11 patients with metastases to lymph nodes had neoplastic invasion of less than 6 mm.

The frequency of invasion of adja-

cent structures also increased with the measured extent of the malignant neoplasm. In all, 27 patients manifested invasion of nerves; 16 (59%) of these patients died of their disease. Involvement of regional bony structures had a more ominous significance. Eight of ten patients with histologic evidence of such an event died of their disease. Eleven (39%) of 28 without such findings also died of their disease.

The effects of extirpative surgery, as assessed by surgical margins, on several aspects of the biologic behavior of the neoplasms are shown in Table 2 for the 36 patients in whom full information was available. Only two of 12 patients with resections manifesting positive margins are surviving without clinical evidence of their neoplasms. Histologically negative margins, however, were not assurances against recurrences, nodal metastases, or death. Eight (33%) of 24 patients whose surgical resection margins were negative still died of their cancer.

The measured gross size of the neoplasms in patients who died of their disease ranged from 1.5 to 14 cm (mean, 5 cm). For those patients living without evidence of clinical recurrence or metastases, the size of their neoplasms ranged from 1 to 9 cm (mean, 5 cm). Correlation between the gross size and measured invasion was not strong; eg, two tumors measuring 1.5 cm in major gross dimension exhibited 12-mm invasions.

The site of origin of the neoplasms did not appear to notably influence outcome. Fourteen (51%) of 26 parotid primary tumors caused death; four of seven palatal tumors did also, and two of three patients with their primary neoplasm in the submandibular gland died of their disease.

Table 3 presents the three modes of therapy used in the study period and compares them with follow-up status.

COMMENT

As indicated by the findings in this study, there is no prototypical carcinoma that arises in or from a mixed tumor. The carcinomas may be histologically low or high grade and they are predominantly ductal in their cytoarchitecture (Fig 6). An absence of carcinomas having the features of an adenoid- cystic, acinic cell, or mucoepidermoid carcinoma also strengthens our conviction that it is most unusual for these carcinomas to arise in mixed tumors.

Of the several indexes used to correlate with clinical course, the following two are new: histologic subtyping of the malignant neoplasm and the objective measurement of invasion. Taken as an independent variable, histologic classification appears to be an important determinant of prognosis (Table 4). The five-year survivals based on the type of malignant neoplasm are as follows: 0% for true malignant mixed tumors, 30% for undifferentiated carcinomas, 50% for myoepithelial carcinomas, 62% for ductal carcinomas; and 96% for terminal duct carcinomas arising in mixed tumors.

The two quantitative markers, gross size of tumor and measurable invasion by the malignant neoplasm, give different degrees of reliability. Malignant mixed tumors appear to be an exception in the ability to relate size of tumor to biologic behavior of malignant tumors of salivary tissues. In our material, as well as in the published series of others,[1] no definite association between gross dimensions of the tumor and incidences of recurrence or metastases could be made. The most likely explanation is that gross size of malignant mixed tumors does not always indicate the size of the malignant component. Proportions of benign to malignant areas vary considerably. In some large neoplasms, the preponderant tissue is benign mixed tumor; in others, only microscopic foci of the residual benign tumor is present.

The measured invasiveness by the malignant components of malignant mixed tumors in the series gives a strong correlation with outcome. No patients died of their disease when invasion was less than 6 mm. All patients whose malignant neoplasm extended for more than 8 mm died as a consequence. It is important to note that only one of nine histologically low-grade (terminal duct) carcinomas manifested invasion of more than 8 mm. In our case material, the measurable extent of the malignant neoplasm also correlates with the presence or absence of tumor at surgical margins, presence of perineurial invasion, bone and lymph node involvement, and incidence of recurrence.

Of the four clinicopathologic categories of malignant mixed tumor, the intralesional or in situ carcinoma ex pleomorphic adenoma and the benign metastasizing mixed tumor were not found in this series. As indicated before, the latter is a medical curiosity. Some of the eight cases recorded in the literature through 1978 demonstrated an infiltrative growth pattern and increased mitoses.[3] Recurrences and repeated surgical manipulations may play a role in their hematogenous spread. According to LiVolsi and Perzin,[4] the clinical behavior of the in situ carcinoma (no invasion of capsule or adjacent stroma) does not differ from that of a benign mixed tumor.

Three of our malignant neoplasms were the rarely reported (Table 5) true malignant mixed tumor in which there is a synchronous biphasic neoplasm (sarcoma and carcinoma).[4] They occurred in major (parotid and submandibular) and minor (palate) salivary glands. All displayed a high degree of lethality.

References

1. Spiro RH, Huvos AG, Strong EW: Malignant mixed tumor of salivary origin: A clinicopathologic study of 146 cases. *Cancer* 1977;39:388-396.

2. Johns ME: Parotid cancer: A rational basis for treatment. *Head Neck Surg* 1980;3:132-144.

3. Batsakis JG: Malignant mixed tumor. *Ann Otol Rhinol Laryngol* 1982;91:342-343.

4. LiVolsi VA, Perzin KH: Malignant mixed tumors arising in salivary glands: I. Carcinomas arising in benign mixed tumors: A clinicopathologic study. *Cancer* 1977;39:2209-2230.

5. Moberger JG, Eneroth C-M: Malignant mixed tumor of the salivary glands: Special reference to the histologic structures in metastases. *Cancer* 1968;21:1198-1211.

6. Batsakis JG, Pinkston G, Luna M: Terminal duct carcinoma of salivary tissues, abstracted. *Lab Invest* 1983;48:7.

7. Batsakis JG, Pinkston G, Luna MA, et al: Adenocarcinomas of the oral cavity: A clinicopathologic study of terminal duct carcinomas. *J Laryngol Otol* 1983;97:825-835.

8. *Surveillance, Epidemiology, End Results: Incidence and Mortality Data, 1973-1977*. National Cancer Institute Monograph 57, National Institutes of Health publication 81-2330. Bethesda, Md, US Dept of Health and Human Services, 1981, p 138.

Case 25. Malignant ameloblastoma

The accompanying reprint outlines data on maxillary ameloblastomas. Although your case retained features of a conventional ameloblastoma in its malignant transformation, the more varied appearances of maxillary ameloblastomas continue to cause diagnostic problems for surgical pathologists. In the past six months, I've personally seen six cases miscalled other forms of sinus neoplasms, most often undifferentiated carcinomas.

In addition to the references in the reprint the following articles are valuable in the understanding of malignancy in ameloblastomas.

Anneroth, G., and Hansen, L.S.: Variations in keratinizing odontogenic cysts and tumors. Oral Surg. 54:530-546, 1982.

Elzay, R.P.: Primary intraosseous carcinoma of the jaws. Review and update of odontogenic carcinomas. Oral Surg. 54:299-303, 1982.

Slootweg, P.J., and Muller, H.: Malignant ameloblastoma or ameloblastic carcinoma. Oral Surg. 57:168-176, 1984.

PATHOLOGY CONSULTATION

AMELOBLASTOMA OF THE MAXILLA AND PERIPHERAL AMELOBLASTOMAS

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Ameloblastomas arising in the supraperiosteal soft tissues (peripheral ameloblastoma) and those taking origin in the maxilla have distinctively different biologic behaviors. The peripheral ameloblastoma can be successfully treated by conservative excision while en bloc resection is warranted for the maxillary ameloblastoma. The effectiveness of primary surgical treatment of an ameloblastoma of the maxilla is the key to reduce morbidity and mortality from the lesion. Anatomic differences between the maxilla and mandible and an apparent more aggressive behavior of maxillary tumors also play a role in establishing the ameloblastoma of the maxilla as the most dangerous of the ameloblastomas.

Ameloblastomas comprise approximately 1% of all tumors of the jaws. Twenty percent take their origin in the maxilla where almost half of the lesions are found in the molar region, one third in the area of the antrum and the remainder at other sites, including no more than 2% in the anterior maxilla.[1]

Histogenesis and acceptable methods of treatment continue to be debated for all ameloblastomas, but for those arising in the maxilla and in extraosseous sites there is little ambiguity or ambivalence.[1,2]

The extraosseous or peripheral ameloblastoma shows a distinct mandibular predilection where it occurs in the soft tissues covering the tooth-bearing parts of the jaw. Origin of the peripheral ameloblastoma remains somewhat controversial. Most likely it derives from epithelial rests left from tooth development. These remnants, formerly connections between the enamel organ and the overlying mucosa, lie in the supraperiosteal connective tissue.

In general, the peripheral ameloblastoma lacks the persistent invasiveness of intraosseous ameloblastoma. Adequate management is excision with a small margin of normal tissue and periodic examinations.[2] The apparent effectiveness of simple local excision for peripheral ameloblastomas cannot be transferred to centrally located lesions and especially not to ameloblastomas of the maxilla. "Beware of the maxillary ameloblastoma" should be nearly axiomatic for surgeons and pathologists.

The potentials for disastrous consequences for the patient with an ameloblastoma of the maxilla are of a far greater magnitude than for patients with ameloblastomas of the mandible. In the maxilla, the tumors typically occur in the cuspid and antral areas where at least two factors predispose to local extensions. The bone of the maxilla is structurally different from that of the mandible. The latter's thick and compact bone more readily confines the tumors; this type of bone is absent in the maxilla.[3] Intimacy with the nasal cavity, paranasal sinuses, orbit, pharyngeal tissues, and the vital structures at the base of the skull certainly add a clinical dimension not present for ameloblastomas of the mandible.

Given the above, what additional factors predispose to recurrence and subsequent loss of local control of an ameloblastoma of the maxilla? Although there is insufficient documentation using histologic criteria, there is certainly an indication that ameloblastomas of the maxilla are more aggressive than their counterparts in the mandible.[3,4] Our experience and that of others[5] has been that ameloblastomas of the maxilla tend to a greater cellularity and greater departure from the conventional ameloblastomas. This can be appreciated in Figure 1A, B. Figure 1A, taken from a conventional tumor, illustrates the classic peripheral palisade of cells encompassing islands of stellate reticulum. Figure 1B, taken from an ameloblastoma of the maxilla, illustrates the shortening of the peripheral cells and beginning loss of polarity. In addition, it shows an acanthomatous focus, a finding more often noted in the maxilla.

More significant than histologic appearance, however, is the impact of recurrences following inappropriate primary treatment.[3] The results after curettage are such that that mode of therapy should be condemned. Sehdev et al[3] report a 100% recurrence rate, and worse, a 63% death rate, or life with massive recurrences following curettement of maxillary ameloblastomas. In that context, it is worth requoting Shatkin and Hoffmeister:[6] "The so-called 'conservative' treatment by curettage, at

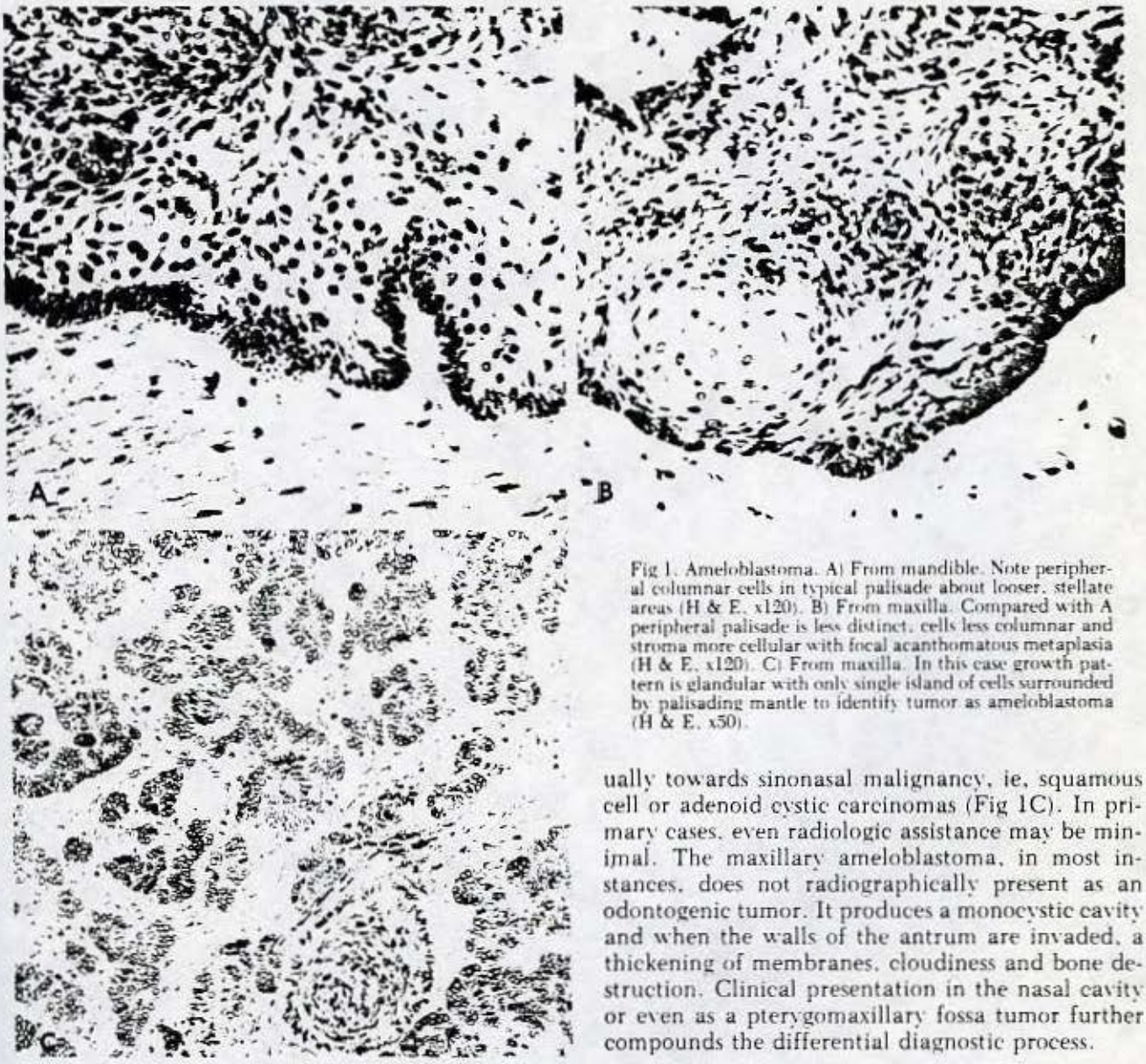

Fig 1. Ameloblastoma. A) From mandible. Note peripheral columnar cells in typical palisade about looser, stellate areas (H & E, x120). B) From maxilla. Compared with A peripheral palisade is less distinct, cells less columnar and stroma more cellular with focal acanthomatous metaplasia (H & E, x120). C) From maxilla. In this case growth pattern is glandular with only single island of cells surrounded by palisading mantle to identify tumor as ameloblastoma (H & E, x50).

best, disfigures the patient and, at worst, kills him, whereas the so-called 'radical' treatment by adequate excision conserves the patient's appearance, function and life." The only rational treatment of a maxillary ameloblastoma is complete en bloc removal with a margin of uninvolved tissue.[3]

From the pathologists' standpoint, ameloblastomas of the maxilla may be difficult diagnostic problems, especially if they are not provided with a history of a preexisting ameloblastoma. Errors are usually towards sinonasal malignancy, ie, squamous cell or adenoid cystic carcinomas (Fig 1C). In primary cases, even radiologic assistance may be minimal. The maxillary ameloblastoma, in most instances, does not radiographically present as an odontogenic tumor. It produces a monocystic cavity and when the walls of the antrum are invaded, a thickening of membranes, cloudiness and bone destruction. Clinical presentation in the nasal cavity or even as a pterygomaxillary fossa tumor further compounds the differential diagnostic process.

SUMMARY

The maxillary ameloblastoma by virtue of its location, apparently more aggressive behavior, and inadequate treatment, can be a lethal lesion. This contrasts with the usual behavior of ameloblastomas of the mandible and sharply from the peripheral ameloblastoma. Unfamiliarity with the lesion on the part of pathologists may lead to overdiagnosis, for example, squamous cell or adenoid cystic carcinomas.

REFERENCES

1. Goodsell JF, Yamashita D-D, Moody R. Ameloblastoma of the anterior maxillae. J Surg Oncol 1977; 9:407-16.

2. Gardner DG. Peripheral ameloblastoma: a study of 21 cases, including five reported as basal cell carcinoma of the gingiva. Cancer 1977; 39:1625-33.

3. Sehdev MK, Huvos AG, Strong EW, Gerold FP, Willis GW. Ameloblastoma of maxilla and mandible. Cancer 1974; 33:324-33.

4. Mehlisch DR, Dahlin DC, Masson JK. Ameloblastoma: a clinicopathologic report. J Oral Surg 1972; 30:9-22.

5. Regezi JA, Kerr DA, Courtney RM. Odontogenic tumors: analysis of 706 cases. J Oral Surg 1978; 36:771-8.

6. Shatkin S, Hoffmeister FS. Ameloblastoma: a rational approach to therapy. Oral Surg 1965; 20:421-35.