1487

CALIFORNIA TUMOR TISSUE REGISTRY

97TH SEMI-ANNUAL CANCER SEMINAR

# "SELECTED DIAGNOSTIC PROBLEMS IN SURGICAL PATHOLOGY"

## CASE HISTORIES

PRELECTORS:


**Stacey E. Mills, M.D.**
Professor of Pathology
Associate Director of Surgical Pathology
University of Virginia Health Science Center

and

**Robert E. Fechner, M.D.**
Professor, Director of the Division of Anatomic Pathology
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December 4, 1994
San Diego Marriott Hotel and Marina
San Diego, California

CHAIRMAN:


**Franco Bertoni, M.D.**
Director of Surgical Pathology
Malpighi Hospital and Rizzoli Orthopaedic Institute
Associate Professor of Pathology
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**Stacey E. Mills, M.D.**
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## CASE HISTORIES:

Case #1 (Accession 22916): In the Spring of 1978, this 65-year-old male presented with intermittent, terminal hematuria of approximately one month's duration. Cystoscopy demonstrated a tumor involving the anterior bladder wall. A segmental cystectomy was performed. (Contributed by E. R. Jennings, M.D.)

Case #2 (Accession 23087): A 49-year-old man presented for medical evaluation with a painful mass of two months' duration in his left thigh. Radiographs showed no evidence of osseous involvement. An incisional biopsy was performed. This was followed by a supra-acetabular amputation of his left leg. (Contributed by Horace Spear, M.D.)

Case #3 (Accession 26494): An 81-year-old man had a history of a total laryngectomy in 1986 for squamous cell carcinoma and a transurethral prostatic resection in July, 1988, for benign prostatic hypertrophy. Six months later, a 2.5 cm mass was noted in the soft tissues of his right hip. An excisional biopsy was performed. (Contributed by Dong Quach, M.D.)

Case #4 (Accession 27601): A 16-year-old boy fractured his distal femur while playing football. Radiographs documented a fracture of the distal femoral metaphysis. In addition, an ill-defined permeative, lytic lesion was noted in the mid-shaft of the femur, with an overlying periosteal reaction. An amputation was performed. (Contributed by Stacey Mills, M.D.)

Case #5 (Accession 18700): A 14-year-old girl complained of pain in her neck and right arm of "long duration." Radiographs showed collapse of the sixth cervical vertebral body, possibly due to neoplasm. A biopsy was performed, leading to a diagnosis of fibrous dysplasia. This was followed by curettage and bone grafting. She did well for 10 years, and then developed recurrent symptoms of pain and numbness in the neck and arm, with difficulty swallowing and a "bony hard" neck mass. Radiographs demonstrated a "honeycomb" bony mass to the right of the midline of C6-C7, in the region of the prior cervical fusion. A second local resection with vertebral fusion was performed, and the patient has apparently been disease free for the subsequent 24 years. (Contributed by Harlan Fulmer, M.D.)

Case #6 (Accession 24499): A 28-year-old woman had pain in the left arm and shoulder of uncertain duration. An X-ray disclosed a large lytic lesion in the mid shaft. There was a pathologic fracture. (Contributed by Aaron A. Dubrow, M.D.)

Case #7 (Accession 27588): A 22-year-old man had pain in the left part of his face for about two weeks. An X-ray showed opacification of the left antrum. CT-scans demonstrated destruction of the anterior wall of the antral bone. (Contributed by Robert E. Fechner, M.D.)

Case #8 (Accession 27453): A 38-year-old woman had swelling and pain in her left knee for several months. She had been operated upon before and had arthroscopic removal of synovial tissue. The diagnosis is unknown. At the time of the present surgery, 36 grams of tan, brown and white tissue fragments were removed that measured 6.0 x 5.0 x 1.5 cm in aggregate. (Contributed by Boleslaw H. Liwnicz, M.D., Ph.D.)

Case #9 (Accession 25253): A 62-year-old man had a mass in his left wrist of several years duration. It was painless and perhaps had enlarged slightly over that time. There was no evidence of bone abnormality. (Contributed by Wafa Michael, M.D.)

Case #10 (Accession 24404): An 83-year-old man complained of nasal stuffiness. Radiographic examination showed no destruction of bone, although the right maxillary antrum was opacified. There was no evidence of bone invasion at the time of surgery. His prior history included excision of "nasal and sinus tumors" in 1974, but the material is unavailable. (Contributed by Albert Garib, M.D.)

Case #11 (Accession 27494): A 62-year-old man presented with a mass involving the region of his right tonsil. A local excision and radical neck dissection were performed. (Contributed by Michael Kanter, M.D.)

Case #12 (Accession 27454): A 47-year-old woman with a history of sarcoidosis presented with a mass in the left side of the soft palate which had been present for four years. The clinical impression was a benign tumor of minor salivary gland origin. She underwent wide local excision of the mass with placement of a palatal prosthesis. (Contributed by Arthur Hauck, M.D.)

Case #13 (Accession 27474): A 6-year-old boy had a one-month history of recurrent epistaxis, a ten pound weight loss and decreased appetite. Radiographic study showed a large nasopharyngeal mass with extension into the right anterior cranial fossa. An incisional biopsy of the nasopharyngeal mass was performed. (Contributed by G. W. Saukel, M.D.)

Case #14 (Accession 12930): A 41-year-old woman presented with nasal obstruction of approximately six months' duration. On physical examination, the upper portion of the nasal cavity was completely filled by a large, deep red, granular tumor which bled easily. The mass extended through the posterior choanae, into the nasopharynx and grew downward, obstructing the right Eustachian tube opening, and displacing the soft palate. (Contributed by Carter Alexander, M.D.)

Case #15 (Accession 27501): A 72-year-old woman present with a 3-month history of tenesmus with decreasing stool caliber. Colonscopy demonstrated an intraluminal adenocarcinoma. Abdominal CT-scan showed an "omental cake" and diffuse abdominal metastases. Ascites were also noted. She had an abdominal hysterectomy and unilateral salpingo-oophorectomy a number of years earlier. At the time of laparotomy, tumor diffusely involved the serosal surfaces of the abdomen, with extension through the colon in the region of the sigmoid. The omentum was densely replaced by tumor. The remaining right tube and ovary had serosal involvement by tumor. A debulking procedure was performed. (Contributed by G. W. Saukel, M.D.)

Case #16 (Accession 25060): A 36-year-old woman had an irregular mass in her breast. A 4.0 x 3.0 x 2.0 cm area of firm tissue was removed that contained two cysts measuring less than 1 cm in diameter. (Contributed by Douglas W. Andorka, M.D.)

Case #17 (Accession 14660): A 38-year-old woman noted a mass in the upper portion of the right breast. Al ill-defined mass was palpated, and a biopsy was performed. A 2.5 cm specimen was removed that showed soft, white fibrous tissue intermixed with fat. There was no discrete lesion. (Contributed by W. Harriet Davis, M.D.)

Case #18 (Accession 27586): A 33-year-old woman had calcifications suspicious for carcinoma in-situ. The suspicious area was excised and there was no gross abnormality. A 4.0 x 3.5 x 3.5 cm piece of tissue included several soft white fibrous areas without a discrete lesion. The block including the calcification was identified and showed changes no different than present on the slides available for study. (Contributed by Robert E. Fechner, M.D.)

Case #19 (Accession 27493): A 57-year-old nulliparous woman had a mass in her right breast. She did not know how long it had been present. On palpation it was firm, measured approximately 3 cm in diameter, and it was thought to be invasive carcinoma by the surgeon. An excisional biopsy disclosed a 2.8 cm firm, white lesion with yellow streaks. It had an ill-defined margin. The patient had a prior history of a breast biopsy in 1982. The slides are not available, but this was described as having a spindle cell proliferation, papillomatosis, and intraductal papillomas, plus complex sclerosis. It is said to have been "similar to the present lesion". (Contributed by Joseph N. Carberry, M.D.)

Case #20 (Accession 25771): A 29-year-old woman had a breast mass removed in 1982. No further therapy was carried out at that time, and she was admitted in 1987 with another mass in the same area. This mass had increased rapidly in size during the previous three months, and it now measured approximately 7.0 cm in size. It was excised. (Contributed by E. W. Wasef, M.D.)

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# ADDENDA

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# SELECTED DIAGNOSTIC PROBLEMS IN SURGICAL PATHOLOGY
# 97TH SEMI-ANNUAL CANCER SEMINAR

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## CASE #1

**History.** In the Spring of 1978, this 65 year old male presented with intermittent, terminal hematuria of approximately one month's duration. Cystoscopy demonstrated a tumor involving the anterior bladder wall. A segmental cystectomy was performed.

**Diagnosis.** Small Cell Undifferentiated Carcinoma (SCUC) of the Urinary Bladder

**Follow-up.** Nine years later the patient developed signs of urinary obstruction. A prostatic adenocarcinoma (Gleason score 7) was detected. This tumor did not resemble the prior bladder tumor and there was no evidence of recurrent bladder neoplasm. The patient was alive and disease free, as of 15 years after the diagnosis of his bladder tumor.

**Gross Microscopic Features.** In the resection specimen, the tumor measured 5.5 x 4.5 x 3.0 cm and apparently extended through the bladder musculature. The overlying serosal surface was free of tumor.

**Light Microscopic Features.** SCUC of the urinary bladder is microscopically indistinguishable from its far more common pulmonary counterpart. The tumors deeply invade the bladder musculature, commonly with complete penetration and extension into the surrounding perivesicular fat. The typical growth pattern consists of nests, ribbons and sheets of cells. Rosette-like structures may be present. Necrosis is invariably seen and varies from small foci to larger areas of infarct-like necrosis. Vascular invasion is also common and occasional examples will show hematoxylin-staining deposits around blood vessels (Azzopardi effect). Cytologically, the tumors consist of a mixture of "oat-like" and intermediate cells. The former have small, uniform, often elongated, densely hyperchromatic nuclei. The latter have larger nuclei with coarsely stippled to, occasionally, vesicular, nuclei. Nuclear molding and "squash" artifact is common, particularly in areas of oat-like cells. Mitotic figures are invariably abundant.

In our study, 8 of 12 (75%) tumors contained small foci (<10%) of other forms of carcinoma (11). Seven had transitional cell neoplasia, 3 had foci of squamous cell carcinoma, and three had foci of adenocarcinoma. One tumor contained a spindle cell, sarcomatoid carcinoma component, and one contained a focus of moderately differentiated neuroendocrine carcinoma ("atypical carcinoid tumor") (11). Grignon et al. reported other forms of neoplasia in 23% of their bladder SCUC (6). Blomjous et al. found such foci in 39% of their cases (2).

**Immunohistochemistry.** SCUC of the urinary bladder show variable epithelial and neuroendocrine features at the immunohistochemical level (2,6,11,14,16). The following table gives approximate rates of positivity for various markers applied to these tumors:

**SCUC OF URINARY BLADDER**
**Immunohistochemical Features**

| REAGENT | % Positive Cases |
|---|---|
| Cytokeratin | 60%-90% |
| EMA | 67% |
| NSE | 83% to 100% |
| Synaptophysin | 67% |
| Neurofilament | 60% |
| Chromogranin | 25% |
| Leu-7 | 58% |
| S-100 Protein | 0%-40% |
| Vimentin | 0% |
| LCA | 0% |

NSE shows the strongest and most consistent staining. Cytokeratin positivity is often focal and, in many instances, has a punctate perinuclear pattern analogous to that seen in neuroendocrine tumors arising in other locations. The above table refers only to the SCUC component of composite tumors.

**Clinical Features.** SCUC of the urinary bladder is predominantly a neoplasm of older individuals, with over half being 70 years of age or older at the time of diagnosis (2,4-9,11,13-17,21). In our series of 12 patients there was a striking male predominance (10 males, 2 female) (11). Other series have also shown a strong male (2 to 1) predilection (2,6,16). Hematuria is the most common presenting complaint. (6,11). A minority of patients will have a history of prior transitional cell carcinoma, but for most their SCUC is their first bladder neoplasm.

Treatment of SCUC of the urinary bladder usually consists of radical surgical resection with adjuvant chemotherapy and/or radiation therapy.

In one series, the five year survival rate was 35% (6), and in our study five of eight patients with long-term follow-up were dead of disease with a median interval to death of only 4 months. Three patients were living with unresectable disease (11). One study showed no significant correlation between stage and survival (6), but others have suggested that survival does correlate with stage, and that SCUC is potentially curable (16). In their study and review, tumors confined to the bladder had a one-year survival rate of 75% (16). Even more recent studies have suggested that aggressive chemotherapy, following radical surgery, may result in somewhat improved long-term survival (2,13).

Rare SCUC of the bladder have been associated with ectopic hormone production, including ACTH and calcitonin (15,17).

## DIFFERENTIAL DIAGNOSIS

**Carcinoid Tumor.** As in other locations the spectrum of neuroendocrine neoplasia of the urinary bladder includes a better differentiated, carcinoid-like neoplasm (3). The latter tumors are even more rare, than SCUC of the bladder, however. Colby reported a single example in a 30 year old male (3). The tumor was histologically identical to typical bronchial carcinoid tumors, and the patient was disease free after resection with only a one-year follow-up. The tumor was easily distinguished from SCUC, based on its much larger, better differentiated cells forming organoid structures. Mitotic figures were rare and there was no necrosis. The existence of neoplasms intermediate between typical carcinoid tumor and SCUC of the urinary bladder has not been well documented. One SCUC in our series did have a focus of better differentiated neuroendocrine neoplasia which resembled so-called "atypical carcinoid tumor" of the lung.

**Paraganglioma.** Although unlikely to be confused with SCUC on light microscopic features, the neuroendocrine staining of a urinary bladder paraganglioma may lead to confusion with carcinoid tumor or other neuroendocrine carcinoma. Paragangliomas of the urinary bladder are rare neoplasms with light microscopic features and biologic behavior identical to those of paragangliomas arising in more typical locations. Urinary bladder paragangliomas will express NSE, and a wide variety of amine and polypeptide hormones (12). The sustentacular cells are frequently S-100 protein positive. Cytokeratin and EMA staining is invariably negative. The latter finding is helpful for distinguishing paragangliomas from carcinomas, regardless of the site of origin.

**SCUC of Prostatic Origin.** The distinction between high-grade transitional cell carcinoma of the bladder and high-grade prostatic adenocarcinoma is often difficult. This problem is even more severe with regard to SCUC because, the prostate gland may also give rise to SCUC which are microscopically identical to their urinary bladder counterparts (18,20). Over half of such cases will be associated with areas of more conventional prostatic adenocarcinoma, and this finding will greatly aid in the diagnosis of a prostatic primary. The majority of prostatic SCUC will be negative for PSA or PAP, but about 17% will express this marker (18) Thus, positivity for PSA or PAP is helpful in supporting prostatic origin, but negativity is of no value. The best distinguishing criteria are probably those based on careful clinical and radiographic evaluation of the tumor epicenter.

**Malignant Lymphoma.** The distinction of bladder SCUC from lymphoma is extremely relevant, clinically, and is easily accomplished with the use of antibodies against leukocyte common antigen in addition to a panel of epithelial markers. Lymphomas of the urinary bladder are distinctly rare neoplasms (1,10,19).

**Transitional Cell Carcinoma.** In our experiences, the distinction between poorly differentiated transitional cell carcinoma (TCC) and SCUC is not typically difficult. Although high-grade TCC may have a sheet-like growth pattern, it is composed of considerably larger cells with more prominent cytoplasm. The presence of neuroendocrine differentiation in immunohistochemical preparations may be helpful in rare cases where this distinction is problematic.

There are rare subtypes of TCC which may be somewhat more difficult to distinguish from SCC. Zukerberg and colleagues described a lymphoepithelioma-like, undifferentiated or high-grade TCC with features indistinguishable from

those of nasopharyngeal lymphoepithelioma (22,23). Unlike SCUC of the bladder, the cells were larger, with more obvious cytoplasm. The nuclei were chromatically uniform and vesicular, rather than the more typical hyperchromatic nuclei seen in most SCUC. The carcinoma cells in this variant may be very widely separated in the reactive lymphoid component, but will stain for epithelial markers (23).

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## CASE #2

**History.** A 49-year-old man presented for medical evaluation with a painful mass of two months' duration in his left thigh. Radiographs showed no evidence of osseous involvement. An incisional biopsy was performed. This was followed by a supra-acetabular amputation of his left leg.

**Diagnosis.** Epithelioid Sarcoma

Epithelioid sarcoma was first described in detail by Enzinger in 1970 (8). Subsequent studies have emphasized the clinical and light microscopic features of this tumor (2,3,17,18). These studies have repeatedly emphasized the considerable diagnostic challenge which this tumor can provide.

**Follow-up.** The patient received postoperative chemotherapy. Over the ensuing six months, he developed progressive shortness of breath with radiographic evidence of extensive pulmonary metastases. He died with respiratory failure and an autopsy documented extensive pulmonary parenchymal and pleural metastases.

**Microscopic Features.** The classic microscopic appearance of epithelioid sarcoma is one of nodular aggregates of epithelioid cells with prominent eosinophilic cytoplasm, surrounding a central zone of less cellular collagen, often with areas of central necrosis. Neoplastic, multinucleated giant cells may be present, and there is invariably a spindle cell population. The resultant image superficially resembles a granuloma. There is considerable variation, however, in the spectrum of appearances which these tumors may assume, and there is a tendency for less diagnostic patterns to occur in older, recurrent, or metastatic lesions. In the latter, the tumor often grows as sheets of epithelioid to spindled neoplastic cells

On higher magnification, the epithelioid cells of epithelioid sarcoma exhibit mild to moderate nuclear pleomorphism. Even in minimally pleomorphic cases, the degree of such change is sufficient to distinguish the lesion from a true granuloma. In some examples of epithelioid sarcoma, the epithelioid cells have prominent, glassy eosinophilic cytoplasm which may distort the nucleus peripherally, in a signet-ring-like pattern. The glassy quality to the cytoplasm is due to the aggregation of large numbers of intermediate filaments, primarily vimentin and cytokeratin (see immunohistochemistry) (4,11,14). A gradual, non-abrupt transition from the epithelioid to the spindle cell component is typical. A variable lymphoid infiltrate is present and, in some cases may be marked, mimicking a lymph node.

Stromal mucin may be present in the background, but epithelial mucin production is absent (3). Iron stains may highlight areas of hemosiderin, particularly within necrotic, granuloma-like nodules.

**Immunohistochemical Features.** Properly performed and interpreted immunohistochemical stains can be of great value in arriving at the correct diagnosis. Conversely, lack of awareness of the staining "quirks" of epithelioid sarcoma may compound the diagnostic confusion often surrounding these tumors. The following is a composite of the literature regarding the immunohistochemical phenotype of these tumors (1,3-5,13,16,19,20):

| REAGENT | % Positive Cases |
|---|---|
| Vimentin | 95-100% |
| Cytokeratin | 75-95% |
| EMA | 60% |
| CEA | 28-38% |
| Ulex europeaus | 75% |
| MS Actin | 28-73% |
| S100 Protein | 7-8% |
| CD34 | 50% |

Epithelioid sarcomas are, in addition, notably negative for leukocyte common antigen, myoglobin, Factor VIII-related antigen, B72.3 and HMB-45 (1,13,19). Staining for cytokeratin, EMA, and CEA, taken out of context, may lead to confusion with a carcinoma. Likewise, staining for MSA and S100 protein may lead to confusion with rhabdomyosarcoma or malignant melanoma (see Diff. Dx. below). Intermediate filament heterogeneity in the form of mixed vimentin/cytokeratin expression is a common and diagnostically helpful feature of these tumors. Such heterogeneity may progress in evolving disease, however, as typified by the metastases in one case that also expressed neurofilaments (11). Epithelioid sarcoma is one of a group of soft tissue sarcomas, also including

synovial sarcoma and extra-renal rhabdoid tumor, characterized by the typical co-expression of cytokeratin and vimentin in relatively large, diagnostically useful amounts. A much larger group of sarcomas, including leimyosarcomas, anglosarcomas, and others, is known to occasionally express much smaller amounts of cytokeratin.

Clinical Features. Epithelioid sarcoma presents in patients from 4 to 90 years of age (3). About 75% are in their second to fourth decades of life (3). There is a male predominance of almost two to one (3). Most patients present with a firm to hard mass in the deep soft tissue, subcutis, or dermis. Occasionally, the lesion presents as a cutaneous ulceration, unresponsive to antibiotic therapy. Pain is present in a minority (22%) of cases (3). Patients are typically symptomatic for several years prior to diagnosis, with some individuals symptomatic for a decade or more. About 20% of patients give an unsolicited history of prior trauma to the tumor site, ranging from immediately to decades earlier. In the large series of 241 cases from the AFIP (3), the tumors were distributed as follows:

| LOCATION | % of CASES |
|---|---|
| Distal upper extremity | 58% |
| Distal lower extremity | 15% |
| Proximal lower extremity | 12% |
| Proximal upper extremity | 10% |
| Trunk | 3% |
| Head & neck | 1% |

About 24% of cases involved the skin and 28% extended into underlying skeletal muscle (3).

Following initial surgical resection, about 75% of patients develop local recurrences. These are often multiple and typically arise proximal to the prior resection site. About half of patients develop metastases (3), most commonly to regional lymph nodes (48%) and lungs (3). Ultimately, over half of patients with metastases had lung involvement. In general, the more proximal extremity and trunk lesions had higher rates of metastasis (3). Overall, 31% of patients died of disease, with a mean follow-up interval of over six years (3). Factors affecting prognosis included sex (females had a better prognosis), age at diagnosis (better in younger patients), small tumor size (no fatalities for tumors <1 cm), high mitotic rate, tumor necrosis, and vascular invasion.

Flow Cytometry / DNA Studies. In one study of 20 epithelioid sarcomas, 12 tumors (60%) were diploid, seven (35%) were aneuploid, and one was tetraploid (7). Ploidy status, or other features such as mitotic rate, did not correlate with prognosis (7). In a separate study of three probable cases, all tumors were diploid and one was noted to show trisomy-2 (15). There is some question, however regarding the distinction between epithelioid sarcoma and extra-renal rhabdoid tumor in this study.

## DIFFERENTIAL DIAGNOSIS

**Granuloma Annulare.** Epithelioid sarcoma may be confused with any granulomatous process. Because of its often necrotic center, a necrobiotic granuloma such as a rheumatoid nodule or granuloma annulare is often suggested. The increased pleomorphism and true necrosis, rather than necrobiosis, of epithelioid sarcoma should allow distinction. The cytokeratin positivity of the latter tumors is also a key distinguishing feature (23).

**Metastatic Carcinoma.** The polygonal cells of epithelioid sarcoma may easily be confused with a metastatic carcinoma and the cytokeratin positivity of the neoplastic cells will add to the diagnostic confusion. The characteristic granuloma-like appearance and transition from epithelioid to spindled cells may be helpful diagnostic features. The subcutaneous or deep location of the tumor, with a lack of an overlying cutaneous component is also helpful. Arber and colleagues emphasized the value of CD34 positivity, seen in about half of epithelioid sarcomas, but rarely found in carcinomas (1).

**Rhabdoid Tumor.** The concept of extra-renal rhabdoid tumor has come under considerable debate, and its status as an "entity" remains clouded. Although many different neoplasms may exhibit a rhabdoid phenotype, there are soft-tissue

tumors which are indistinguishable at light microscopic, electron microscopic, and immunohistochemical levels from their renal counterparts. Such tumors also co-express vimentin and cytokeratin, but are typically easy to distinguish from epithelioid sarcoma, being composed of sheets of much smaller cells with vesicular nuclei, often prominent nucleoli, and variable amounts of cytoplasm. Nonetheless, in some anatomic areas such as the pelvis and vulva confusion between epithelioid sarcoma and "extra-renal rhabdoid tumor" continues (10,21).

**Epithelioid Hemangioendothelioma.** Both epithelioid sarcoma and hemangioendothelioma may be composed of sheets and nests of polygonal cells with prominent eosinophilic cytoplasm. Both tumors may contain prominent cytoplasmic vacuoles. The granuloma-like pattern of epithelioid sarcoma is not seen in hemangioendothelioma, but this may not always be present in the former tumors. Immunohisto-chemistry, if improperly interpreted, may add to the diagnostic confusion. Although almost all epithelioid sarcomas are cytokeratin positive, some hemangioendotheliomas have also been shown to express cytokeratin (12,22). Furthermore, CD34, a marker of endothelial differentiation, is present in approximately half of epithelioid sarcomas (1,20), and *Ulex europeaus* lectin, another endothelial marker is seen in about 75% of epithelioid sarcomas (24). Epithelioid sarcomas lack more specific endothelial markers such as Factor VIII-related antigen and CD31 (6,24).

**Synovial Sarcoma.** These tumors share certain similarities with epithelioid sarcoma and, indeed, some authors have lumped the two under the rubric of tenosynovial sarcoma, an approach which I do not follow. Both strikingly co-express cytokeratin and vimentin. Biphasic synovial sarcomas lack the gradual transition from polygonal to spindled cells that typifies epithelioid sarcoma, and, instead have abrupt transitions between the two components. The spindled cell component of synovial sarcoma often has a fusiform, fibrosarcoma-like or hemangiopericytoma-like pattern, an image not encountered in epithelioid sarcoma. Chase and Enzinger noted that the CEA reactivity seen in up to one-third of epithelioid sarcomas was less common in synovial sarcomas (1 in 7 positive) (3).

**Malignant Melanoma.** Amelanotic malignant melanomas may closely mimic epithelioid sarcomas, in addition to a bewilderingly wide variety of other neoplasms. A small number of epithelioid sarcomas will express S100 protein (7-8%), but these tumors are HMB-45 negative. Cytokeratin expression in malignant melanoma is extremely uncommon, but does rarely occur (9,25).

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## CASE #3

**History.** An 81-year-old man had a history of a total laryngectomy in 1986 for squamous cell carcinoma and a transurethral prostatic resection in July 1988 for benign prostatic hypertrophy. Six months later, a 2.5 cm. mass was noted in the soft tissues of his right hip. An excisional biopsy was performed.

**Microscopic Features.** The mass is predominantly composed of patternless sheets of cells. In some sections, the tumor has a focally nodular growth pattern and appears to be centered in the subcutaneous tissue. Where it can be appreciated, the tumor margin is sharply demarcated from the surrounding tissues. The most prominent cell component consists of spindled cells having moderate amounts of amphophilic, focally vacuolated cytoplasm. There is a background population of slightly larger, more polygonal cells. The latter have a uniform, vesicular chromatin pattern with enlarged nucleoli. These cells bear a striking resemblance to ganglion cells. Mitotic figures are readily appreciated, but unequivocally atypical forms are not identified. There are multiple, microscopic areas of necrosis, with the proliferating cells showing no spatial orientation with respect to these foci. Scattered inflammatory cells, particularly neutrophils, are present as an additional background component.

**Immunohistochemical Features.** Antibodies against muscle specific actin and smooth muscle actin stain blood vessels and scattered, small spindled cells located throughout the lesion. The larger, polygonal cells are negative. Antibodies against desmin, cytokeratin (a broad spectrum cocktail), and S100 protein are also completely negative. The larger, polygonal cells label strongly with antibodies against vimentin. MAC387, an antibody directed against the L1 antigen (2) shared by neutrophils, some squamous cells, and some histiocytes, stains scattered neutrophils only. KP1 antibody against CD68, another histiocyte marker (1), labels scattered, medium-sized polygonal cells resembling histiocytes. Rare, larger cells show some staining with this marker, but the vast majority are negative.

**DIAGNOSIS.** Proliferative fasciitis

The microscopic appearance of this tumor is initially quite alarming and led to consideration of a variety of malignancies, distinction from which is discussed in more detail below. Keys to the correct interpretation of the lesion include its small size, relatively superficial location, rapid growth, and cytologically uniform, albeit disquieting, appearance. Proliferative fasciitis / myositis has been recognized as one of a group of "pseudomalignant" reactive processes for several decades (4,9,10). Recently, the spectrum of this proliferation has been expanded to include more cellular lesions with focal necrosis (12). Seven of 11 cellular variants were initially diagnosed as sarcoma, often leading to aggressive surgical and adjuvant therapy. There is no evidence that these more cellular variants behave differently from more conventional forms. Recurrence is vanishingly rare (4).

Proliferative fasciitis / myositis most commonly involves the extremities. The role of trauma in the development of this lesion in general and the current case in particular is of interest. In the original description of the entity, an association with prior injury was clearly indicated (10). In the subsequent report of intramuscular examples from the AFIP, 9 of 23 patients (39%) with available history indicated prior trauma (9). This was followed by the AFIP description of more superficial (fasciitis) examples, with 10 of 33 (30%) indicating prior trauma (4). In the more recent study of cellular "childhood" variants, only one of 11 patients had a definite history of trauma (12).

Several studies have addressed the ultrastructural and immunohistochemical features of proliferative fasciitis / myositis. All have failed to document true neural or striated muscle differentiation in the ganglion-like cells. The spindled stromal cells have, as in the current case, been noted to show myofibroblastic features, including patchy labelling for actin (7,11). Several studies have suggested weak actin or myosin positivity in the ganglion-like cells, as well (7,12,15). Others, however, have noted a lack of any myogenous staining, with a variety of markers, in the ganglion-like component (3,11). Meis and Enzinger documented focal staining for CD68 in the ganglion-like cells, suggesting histiocytic differentiation (12). The majority of ganglion-like cells stain only for vimentin, however.

Not surprisingly, flow cytometric studies have documented the diploid nature of the cells in proliferative fasciitis / myositis (8,11). Of somewhat more interest, Dembinski et al. noted trisomy 2 as an isolated, clonal abnormality in an example of

proliferative fasciitis (5). Although originally considered indicative of neoplasia, the authors note that clonal karyotypic abnormalities (trisomy 7) recently have been described in other non-neoplastic tissues. Interestingly, epithelioid sarcoma, an important differential diagnostic consideration (see below) also has been reported with trisomy 2 as the sole cytogenetic abnormality (6,11).

## DIFFERENTIAL DIAGNOSIS

Pleomorphic Rhabdomyosarcoma. Proliferative fasciitis / myositis is often confused with rhabdomyosarcoma. In such cases, the large, ganglion-like cells are misinterpreted as developing rhabdomyoblasts. Immunohistochemical stains are of value in making this distinction. Although focal weak actin positivity may be present in occasional ganglion-like cells of proliferative fasciitis / myositis, true rhabdomyoblasts will show strong staining for muscle specific actin, desmin, myosin, and myoglobin. Vimentin staining may be correspondingly diminished.

Epithelioid Sarcoma. The tendency of proliferative fasciitis / myositis to involve the extremities is similar to the distribution of epithelioid sarcoma. Furthermore, the latter tumor is also composed of larger, epithelioid cells with prominent cytoplasm, as well as smaller spindled cells. Epithelioid sarcomas often exhibit areas of necrosis, as may be seen in the childhood variant of proliferative fasciitis / myositis. In the former tumors, however, there is often granuloma-like rimming of the necrotic foci by epithelioid neoplastic cells. The neoplastic cells of epithelioid sarcoma exhibit, at least focally, considerable nuclear pleomorphism, unlike the remarkable nuclear uniformity seen in proliferative fasciitis / myositis. Immunohistochemically, the epithelioid cells of epithelioid sarcoma exhibit (almost invariably) strong staining for both cytokeratin and vimentin. There may also be focal actin positivity in the spindle cell component. The strong cytokeratin staining is of value in distinguishing this neoplasm from proliferative fasciitis / myositis. Recently, about half of epithelioid sarcomas have been noted to show staining for hematopoietic progenitor cell antigen (CD34), also found in vascular neoplasms (14). This may lead to some confusion with epithelioid hemangioendothelioma, but, in the absence of other vascular markers, CD34 positivity may also be used to support an epithelioid sarcoma diagnosis.

Malignant Fibrous Histiocytoma. Proliferative fasciitis / myositis may be confused with a malignant fibrous histiocytoma having prominent epithelioid cells. As above, the distinction can be made on the basis of the considerable pleomorphism exhibited by this sarcoma. Immunohistochemistry is of less value in this distinction. CD68, present in the current case, has been noted to be present in some studies of MFH (1) and absent in others (13).

Epithelioid Hemangioendothelioma. This tumor is less likely to be confused with proliferative fasciitis / myositis, but it may contain polygonal, epithelial-like cells, potentially causing confusion. A myxoid stroma, stranding of cells, intra- and intercellular lumen formation, and overt vasoformative features are helpful in this distinction. Immunohistochemical staining for endothelial markers including FVIII-related antigen, Ulex europaeus, CD31 and CD34 may also be of value. These tumors may show cytokeratin positivity in occasional cases.

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## CASE #4

**History.** A 16-year-old boy fractured his distal femur while playing football. Radiographs documented a fracture of the distal femoral metaphysis. In addition, an ill-defined permeative, lytic lesion was noted in the mid-shaft of the femur, with an overying periosteal reaction. An amputation was performed.

**Diagnosis.** Ewing's sarcoma of bone (vs. neuroectodermal tumor of bone).

**Follow-up.** The patient received postoperative chemotherapy and was free of disease several years after his resection.

**Microscopic Features.** Classic Ewing's sarcoma consists of broad sheets and large nests of uniform, small, polygonal cells with scanty pale cytoplasm and indistinct cell borders. The nuclei are round to oval with finely dispersed chromatin, some hyperchromasia, and a variable number of mitotic figures. In areas of necrosis, recognizable neoplasm often forms distinctive perivascular cuffs. About 10% of cases will contain rosette-like structures that, in reality, represent necrotic cell "drop out" of a contral cell mass. Reticulin is typically scant, except around blood vessels.

Schajowicz emphasized the presence of cytoplasmic glycogen as a helpful diagnostic feature for Ewing's sarcoma (21). About 75% of Ewing's sarcomas will have prominent cytoplasmic glycogen with the PAS technique, and about 10% will be negative. Fixation in 80% ethanol, rather than formalin, may allow more consistent staining.

In 1980, Nascimento, et al. described 20 cases of Ewing's sarcoma composed of larger cells with more marked variation in nuclear size and shape, a clear or vesicular nucleus, and prominent nucleoli (16). This "large cell variant" can more easily be confused, microscopically, with large cell lymphoma, but the glycogen positivity, reticulin pattern, immunohistochemical features, and ultrastructural findings are similar to those of typical Ewing's sarcoma. There are no radiographic or clinical features to distinguish this large cell variant from typical Ewing's sarcoma.

Telles, et al. emphasized that the uniform histologic appearance of classical Ewing's sarcoma may be altered by therapy. In their autopsy study of patients treated with radiation and chemotherapy, many tumors had a more pleomorphic appearance than was seen initially (27). These tumors had large, vesicular nuclei with prominent nuclear folding, and more prominent nucleoli. Some resembled the large cell variant of Ewing's sarcoma, but others were more bizarre with large cellular forms and multinucleated cells. In spite of their marked cytologic transformation, neoplasms that were initially PAS positive, retained PAS positivity in these more pleomorphic cells (27).

Neuroectodermal tumor of bone was first distinguished from Ewing's sarcoma by Jaffe in 1984 (9). Prior to that time, these tumors had undoubtedly been included with cases of Ewing's sarcoma. In their article, Jaffe and colleagues stated that, "Any clear evidence of differentiation would be incompatible with a diagnosis of Ewing's sarcoma, even though the category of Ewing's sarcoma may undergo progressive attrition as newer techniques are applied" (9). Indeed, as immunohistochemical techniques have progressed, an increasing number of otherwise typical "Ewing's sarcomas" have shown at least some immunohistochemical evidence of neuroectodermal differentiation (see below). How to classify such relatively common cases is currently unclear.

**Can / should we distinguish Ewing's sarcoma and neuroectodermal tumor?** For the moment, at least, attempts at their distinction seem justified, based on several studies which suggest a higher frequency of metastases at diagnosis, an adverse response to treatment and resultant poorer prognosis for tumors with clear-cut neural differentiation as compared to Ewing's sarcoma.

The microscopic appearance of neuroectodermal tumor of bone depends, in part, on how the lesion is defined. It is clear that some tumors light microscopically lacking differentiation and indistinguishable from Ewing's sarcoma may exhibit ultrastructural and immunohistochemical evidence of neuroectodermal differentiation. Typically, such "undifferentiated" areas are composed of small, "blue cells" with scant cytoplasm, round to oval nuclei with evenly dispersed chromatin, and one or more distinct nucleoli (29). Glycogen, as demonstrated by PAS stains, may be present in the neoplastic cells, but tends to be in lesser amounts than is typical of Ewing's sarcoma (9,29,32).

Most neuroectodermal tumors of bone, as currently described, exhibit at least some light microscopic evidence of differentiation, however. Several studies have reported focal Homer Wright rosettes in all cases (9,10,13,24,29), often in association with a fibrillary intercellular background (13). A lobular growth pattern is also common

(9,13), and is best seen with reticulin stains which showed reticular fibers surrounding large groups of cells in a "basket-like" distribution. There is a tendency for cells at the periphery of lobules to be somewhat larger and exhibit evidence of ganglion cell differentiation (9,29). Ganglion cell differentiation may also be present in metastases.

The relationship of Ewing's sarcoma and neuroectodermal tumor of bone has been the subject of numerous publications. Although in many instances, Ewing's sarcoma and neuroectodermal tumor of bone can be distinguished on immunohistochemical and ultrastructural grounds, in some cases the distinction is arbitrary, and where the "line is drawn" varies from study to study (28,29). This difficulty was clearly noted by Jaffe, et al. in their initial description of neuroectodermal tumor of bone and its distinction from Ewing's sarcoma (9). These authors indicated that, "it remains to be shown that the two tumors are clearly and reproducibly separable; it certainly cannot be done on previously published criteria. Ewing's sarcoma may be the most undifferentiated form of the neuroectodermal tumor" (9).

Jurgens, et al. suggested that criteria for the diagnosis of neuroectodermal tumor should include immunohistochemical positivity for neuron specific enolase, in conjunction with clear-cut Homer Wright type rosettes and/or ultrastructural demonstration of dense-core granules (10). Using this approach, neuron specific enolase positivity alone would not be sufficient for exclusion from the category of Ewing's sarcoma. Given the often seemingly nonspecific staining encountered with antibodies to neuron specific enolase, this is a reasonable approach. However, definite positivity for newer, more specific neural antigens such as synaptophysin or neurofilaments is, I believe, sufficient to place a light microscopically undifferentiated but otherwise compatible small cell tumor in the peripheral neuroectodermal category.

Cytogenetic Findings. Multiple cytogenetic studies of Ewing's sarcoma, beginning with the works of Aurias, et al. and Turc-Carel, et al., have clearly documented a characteristic t(11;22)(q24;q12) chromosomal translocation in the cells of Ewing's sarcoma which is present in about 85% of cases (2,18,30,31). A smaller number of cases manifest a deletion from chromosome 22, del(22)(q12). Identical genetic abnormalities have been found in neuroectodermal tumor of bone, the so-called "small cell tumor of the thoracopulmonary region," also known as the Askin tumor, and small cell osteosarcoma (18).

It thus seems likely that Ewing's sarcoma represents the most undifferentiated end of a spectrum of neuroectodermal neoplasms which also includes neuroectodermal tumor of bone, and peripheral soft tissue lesions such as so-called Askin tumor, and peripheral neuroepithelioma (28). This group of lesions seems to be distinct from metastatic neuroblastoma (33).

Immunohistochemical Features. Ewing's sarcoma is, at least currently, more noted for its lack of immunologic staining, than for any characteristic positivity, although this perception is undergoing change. The immunohistochemical profile of Ewing's sarcoma has been the subject of a number of studies, and was recently reviewed by Steiner (24). Vimentin expression is present to varying degrees in the majority, if not all cases. Occasional cases may express cytokeratin, usually in a minority of cells (8,24). Neurofilaments are not typically present (24). Neuron specific enolase and Leu 7, sensitive but not highly specific markers of neuroectodermal differentiation, are usually absent from typical Ewing's sarcoma, at least by the conventional peroxidase-antiperoxidase technique (24,28). Their presence in large quantities in a small blue cell tumor should suggest that the lesion is more likely a neuroectodermal tumor (24,28). This approach is by no means universally accepted, however (32). Furthermore, with the improved sensitivity of the avidin-biotin complex technique for immunoperoxidase staining, NSE, Leu 7, as well as the more neural-specific marker, synaptophysin, are being reported as present in greater numbers of otherwise apparently typical Ewing's sarcoma cells (28,29). Additional studies have documented high levels of the neural marker, choline acetyl transferase, in both Ewing's sarcoma and neuroectodermal tumor (15). These tumors lack the high levels of adrenergic enzymes epinephrine and norepinephrine, as seen in neuroblastoma (28).

Typical Ewing's sarcoma cells are negative for leukocyte common antigen, surface immunoglobulins, lysozyme, alpha-1-antitrypsin, alpha-1-antichymotrypsin, myosin, myoglobin, desmin, and Factor VIII-related antigen (24). Both Ewing's sarcoma and neuroectodermal tumor have been shown to share an overexpression of the pseudoautosomal gene MIC2, located on the short

arms of the sex chromosomes, with the resultant production of large amounts of a specific surface glycoprotein which can be detected by monoclonal antibody HBA-71 (1,11). In a large study of a variety of neoplasms, this antigen was not detected in tumors originating outside of the central nervous system, except for trace staining in a single pancreatic insulinoma (1) Importantly, 12 neuroblastomas lacked staining for this antigen (1).

Results of immunohistochemical staining for neuroectodermal tumor of bone have been somewhat variable owing to differences in technique and progressive improvement in available antibodies and methodology. Results also vary depending on whether immunohistochemical findings are used to ***define*** neuroectodermal tumor, or the tumors are defined by light microscopic, ultrastructural, or molecular biologic techniques, and then studied for their immunohistochemical profile. Combining the results of several studies (9,10,13,26,29) yields the following results:

**PNET Immunohistochemistry**

| Reagent | #positive/#studied or (%) |
|---|---|
| NSE | 61/71 |
| Leu-7 | 14/28 |
| Synaptophysin | 11/14 |
| Neurofilaments | 3/18 |
| Chromogranin | 3/4 |
| S100 protein | 1/18 |
| Vimentin | 100% |
| GFAP | 0% |
| Cytokeratin | 0% |
| Desmin | 0% |
| LCA | 0% |
| HBA-71 / MIC2 | 95+% |

Clinical Features. Of all patients with primary malignant bone tumors, those with Ewing's sarcoma have the youngest average age (7). Eighty percent occur in the first two decades of life with a median age of about 13 years (17). Patients over the age of 30 years are quite uncommon (22). Although Ewing's sarcoma has been described in children as young as 18 months, children under five years of age with small cell neoplasms of bone should be carefully evaluated to exclude metastatic neuroblastoma. Ewing's sarcoma has a definite predilection for males (1.5:1) (7) and is uncommon in blacks.

Localized pain and a mass are the most common symptoms. Most patients give a history of pain for several months prior to the presence of swelling. Some will have generalized symptoms including an increased sedimentation rate, fever, anemia with or without leukocytosis, and malaise. Such findings usually indicate disseminated disease. A minority of patients (about 10%) will have multiple bone involvement at the time of presentation. These probably represent metastases from a single primary, although multiple primaries cannot be excluded. A much higher percentage of patients that develop disseminated disease (about 70%) will have involvement of additional osseous sites later in their course.

The clinical features of patients with neuroectodermal tumor of bone are quite similar in most respects to those of patients with Ewing's sarcoma. Median age is approximately 15 years, and patients have ranged from less than one year to 32 years of age (10,13,20). Most patients are in their first or second decades of life. There is a male predominance of 2-3 to 1. About half will present with fever or other systemic symptoms (20). Approximately one-third will have pathologic fractures (20). Unlike Ewing's sarcoma, between one-half (20) and one-fourth (10) of patients with neuroectodermal tumor of bone will have clinically detectable metastases at the time of initial diagnosis. Metastases have primarily involved bone, lung, and liver, with lymph node involvement being less common.

Many, if not most, so-called "Askin tumors" of the chest wall region represent peripheral neuroectodermal tumors with osseous involvement. If these cases are considered primary osseous neoplasms, then neuroectodermal tumor of bone most commonly involves the ribs, sternum, and vertebra of the chest region. Aggregate cases, excluding rib and chest lesions, from several series (12,13,20,29), had the following distribution: fibula - 26%, tibia - 19%, pelvis - 19%, scapula - 10%, and femur, metatarsal, humerus and radius - 6.5% each. The predilection for the fibula and less common involvement of the femur and humerus is unusual for osseous neoplasia.

## DIFFERENTIAL DIAGNOSIS

Ewing's Sarcoma vs. Neuroectodermal Tumor. The validity and value of this distinction is discussed in detail above.

Small cell osteosarcoma. By definition,

osteoid production must be present in association with small, round to spindled tumor cells (3,14,23). Typically, the osteoid is sparse and has a delicate, "lace-like" appearance. Rare examples of densely sclerotic small cell osteosarcoma have been described. Foci of cartilaginous differentiation are present in at least one-third of cases. Typically, the neoplastic cells grow in sheets and solid nests with densely cellular areas. A focal hemangiopericytoma-like pattern with prominent, branching blood vessels is common. Necrosis is not conspicuous and mitotic figures may be sparse or rare.

Ayala, et al. divided small cell osteosarcomas into three histologic patterns (3). The most common Ewing's sarcoma-like pattern, seen in two-thirds of their cases, consists of round to polygonal cells with densely hyperchromatic nuclei or coarsely clumped nuclear chromatin. Although the nuclei can be uniform, they often exhibit more variation in size and shape than is typically encountered in Ewing's tumors. The second or lymphoma-like pattern consists of cells with slightly larger, more vesicular nuclei and prominent nucleoli. This pattern resembles large cell lymphoma or the large cell variant of Ewing's sarcoma. Small cell osteosarcoma may also consist of closely packed, spindle-shaped cells with only scant amounts of indistinct cytoplasm. Mixtures of these patterns may be seen.

The cells of small cell osteosarcoma may contain cytoplasmic glycogen and, thus, this finding cannot be used for distinction from Ewing's sarcoma. Reticulin stains document an abundant, fine reticulin pattern which surrounds individual cells and small cell groups. There are currently no immunohistochemical markers of value in the diagnosis of small cell osteosarcoma, although they may be used to exclude other possibilities such as lymphoma.

**Mesenchymal chondrosarcoma.** Mesenchymal chondrosarcoma has a highly variable microscopic appearance, both from lesion to lesion and within any given example (5,25). The neoplastic cells may be small, round, oval, or spindle shaped with scant cytoplasm. The nuclei usually have irregular clumping of the chromatin and small nucleoli. Regardless of the shape of the cells, they tend to be only modestly pleomorphic. Mitotic figures are usually sparse, but occasionally may be numerous.

The cartilaginous component of mesenchymal chondrosarcoma is a diagnostic requirement, but is usually only a small percentage of the lesion. This component is cytologically low grade and sharply demarcated from the surrounding stroma. Mesenchymal chondrosarcomas also may contain amorphous, sharply demarcated islands of collagen resembling osteoid. These dense islands lack the delicate, lace-like appearance of the osteoid in osteosarcomas, including the small cell variant. Mesenchymal chondrosarcomas are frequently quite vascular with irregularly anastomosing vessels that impart a nonspecific, hemangiopericytoma-like pattern.

The cartilage islands in mesenchymal chondrosarcoma stain with S-100, whereas the noncartilaginous component does not. Swanson, et al. concluded that the immunophenotype of mesenchymal chondrosarcoma resembles that of embryonic cartilage, but they did not find this especially helpful in the differential diagnosis (25).

**Lymphoma.** The cytologic appearances of osseous large cell lymphoma are identical to those of their far more common nodal counterparts. There is invariably a diffuse growth pattern (4,6), typically with a mixture of small lymphocytic cells, as well as a larger "histiocytic" component. Nuclei exhibit marked variation in shape, with the predominant cells often having grooved or folded, vesicular nuclei and prominent nucleoli. Cytoplasmic glycogen is absent and a complex reticulin framework is typically present in the intercellular background. The latter is somewhat variable, however, and may be lacking in some cases. Intraosseous lymphomas often have a prominent fibroblastic component, and this may be associated with spindling of the neoplastic lymphoid cells. The resultant image may be confused with a spindle cell sarcoma, particularly in suboptimal sections, but application of immunohistochemical stains for lymphoid markers such as leukocyte common antigen should allow distinction. Ostrowski and colleagues noted other diagnostic pitfalls (19). These included cells with clear cytoplasm and signet-ring cells mimicking adenocarcinoma, as well as clustering of neoplastic cells in a pattern resembling carcinoma (19).

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# CASE # 5

**History.** A 14-year old girl complained of pain in her neck and right arm of "long duration." Radiographs showed collapse of the sixth cervical vertebral body, possibly due to neoplasm. A biopsy was performed, leading to a diagnosis of fibrous dysplasia. This was followed by curettage and bone grafting. She did well for 10 years and then developed recurrent symptoms of pain and numbness in the neck and arm, with difficulty swallowing and a "bony hard" neck mass. Radiographs demonstrated a "honeycomb" bony mass to the right of the midline of C6-C7, in the region of the prior cervical fusion. A second local resection with vertebral fusion was performed and the patient has apparently been disease free for the subsequent 24 years.

**Diagnosis.** Osteoblastoma, recurrent

(portions of the following text abstracted from Fechner & Mills (6)).

**Microscopic Features.** Osteoblastomas are hypercellular, haphazard proliferations of fibrovascular tissue and interlacing trabeculae of osteoid (10). The histologic appearance is, in many instances, highly similar to that of osteoid osteoma. It has been suggested that early lesions have a predominance of actively proliferating fibrovascular tissue with numerous giant cells, and only focal osteoid formation. In older lesions, the amount of osteoid increases until it accounts for 50% or more of the lesional tissue (4). There is also considerable intralesional variation with regard to the thickness of the trabeculae and their degree of calcification. Some areas of osteoblastoma may show rather broad sheets of mineralized osteoid with little intervening stroma. More typically, there is a prominent fibrovascular tissue between the islands and trabeculae that has a loose, areolar configuration with prominent, dilated capillaries (10). The osteoblasts are plump, active, and have scattered typical-appearing mitotic figures. Although osteoblastoma may appear highly cellular, there is little or no cytologic atypia in the conventional form. Prominent osteoblastic rimming of the trabeculae is present, at least focally. Osteoclasts may also be numerous along the trabeculae in areas of resorption. Unless there has been a fracture or a previous curettage, osteoblastoma lacks areas of chondroid differentiation (12,15). Osteoblastoma is one of the many tumors which may undergo secondary aneurysmal bone cyst formation (13,19). In one study, of osteoblastomas, such foci were present in 16% of cases (13).

**Discussion.** Osteoblastomas are uncommon osseous lesions, accounting for less than 1% of excised primary osseous tumors and about 3% of benign osseous tumors (4). Although, the distinction between osteoid osteoma and osteoblastoma is usually straightforward, in rare instances it may be arbitrary. Based on the existence of such "borderline" cases and the marked microscopic similarity of osteoid osteoma and osteoblastoma, some authors have advocated combining the two groups, often with subgroup designations such as "circumscribed osteoblastoma" for osteoid osteoma and "genuine osteoblastoma" for the larger lesions (18) or "giant osteoid osteoma" for osteoblastoma (3).

Patients range in age from 3-78 years; 70-90% are less than 30 years of age (8,13). Peak incidence is in the second decade of life. There is a 2 to 1, male to female ratio (8,13). Low-grade, dull, aching pain, often accompanied by tenderness over the tumor site is the most common symptom (13). The duration of pain varies from a few months to several years. Like osteoid osteoma, osteoblastoma of the spine may produce muscle spasm, functional scoliosis or nerve compression, and osteoblastoma of the long bones may lead to muscle atrophy (9,11).

Osteoblastoma shows a distinct predilection for the axial skeleton in general and the spine in particular (2). Approximately 30-50% will occur in the latter location, usually in the posterior elements of the arch and spinous processes. About 30% of osteoblastomas affect the long bones, particularly the lower extremity. About 75% of the long bone lesions are centered in the diaphysis, with almost all of the remainder in the metaphysis (8). In contrast to the typical intracortical location of osteoid osteoma, many osteoblastomas are intramedullary tumors. Rare periosteal osteoblastomas have also been described (7).

The radiographic features are variable and nondiagnostic but usually indicate a benign process. Osteoblastoma produces a uniform, expansile lesion that is well circumscribed and predominantly radiolucent. Older or previously treated lesions may show considerable ossification. Osteoblastoma usually lacks the intense perilesional sclerosis seen in osteoid osteoma.

"Sunburst" or "onion skin" periosteal reactions of the type seen with osteosarcoma are rare. Osteoblastoma does not cross an active epiphyseal plate.

Grossly, intact lesions are well circumscribed and often surrounded by a shell of cortical bone or periosteum. The lesional tissue typically measures 2 to 10 cm. in size (12), and is usually friable and deep red because of its vascularity. Prominent cystic spaces may indicate secondary aneurysmal bone cyst formation.

## DIFFERENTIAL DIAGNOSIS

**Osteosarcoma.** The distinction between osteoblastoma and osteosarcoma is typically straightforward, both radiographically and histologically. However, about 10% of osteosarcomas may appear radiographically benign and, conversely, up to 25% of osteoblastomas may have radiographic features of malignancy (14). Dorfman and Weiss have suggested that problems in distinction between osteoblastoma and osteosarcoma can be divided into four categories (5). The first category is osteosarcomas that histologically bear some resemblance to osteoblastoma (1). The second consists of unusual osteoblastomas that have undergone spontaneous transformation into osteosarcomas. The third category includes very rare clinically and radiographically typical osteoblastomas that show bizarre pseudosarcomatous histologic changes (14,16). Fourth, there are locally aggressive osteoblastomas with distinctive histologic features. For practical purposes, only the first and fourth groups cause diagnostic difficulties. Microscopic features for distinguishing osteoblastoma and osteosarcoma have been well-described by Mirra (15) and similar criteria have been applied by others (1,5).

Intact osteoblastomas, even of the aggressive subtype, rarely if ever produce cartilage. Focal areas of even low-grade cartilage should strongly suggest the possibility of an osteosarcoma. Fractured or previously sampled osteoblastomas may, however, have a reactive chondroid component.

Typical osteoblastomas are composed of thick, irregular trabeculae of osteoid and woven bone. The intervening stroma is about as wide as the osseous component and contains prominent capillaries and osteoclasts. Osteoblastic osteosarcomas more commonly consist of zones of compact osteoid in a tightly knit or streamer pattern with little intervening stroma. Foci with this appearance may be seen in aggressive osteoblastomas, but the osteoblasts in the latter lesion have a characteristic epithelioid appearance (5).

Osteoblastomas and osteoid osteomas show areas of prominent osteoblastic rimming of lesional osteoid. Osteoblastic rimming is distinctly uncommon in the lesional tissue of osteosarcoma, but may be seen in a surrounding reactive component. Although the osteoblasts of osteoblastoma are enlarged and focally mitotically active, with the exception of the rare bizarre osteoblastoma (14,16), they lack the pleomorphism of osteosarcoma and do not contain atypical mitotic figures.

Most importantly, osteosarcomas infiltrate the surrounding lamellar medullary bone, often for several centimeters from the main tumor mass. Osteoblastomas grow with a pushing margin that abuts the host lamellar bone, destroys it, and replaces it with a well-defined tumor margin. Infiltration of woven lesional bone for more than a millimeter or so into the surrounding lamellar bone should strongly suggest a diagnosis of osteosarcoma. Because the nature of this margin may be of such diagnostic importance, biopsies of potential osteoblastomas should include tissue from the periphery of the lesion. Even in curettings, however, it is helpful to look for infiltration in the form of fragments of lamellar bone that have served as a "scaffolding" for the deposition of lesional woven bone. Polarizing filters are of considerable value in making this distinction.

**Osteoid Osteoma.** Osteoid osteoma is rarely confused with osteoblastoma because of its usually clear-cut clinical and radiographic differences. Although the nidus of an osteoid osteoma is quite similar, microscopically, to the lesional tissue of an osteoblastoma, there are minor microscopic differences as documented by Picci and colleagues (17). The periphery of an osteoid osteoma nidus often has a fibrovascular rim, whereas this feature is lacking in osteoblastoma. The latter tumors, in contrast, often have a lobulated or multifocal outer margin. The nidus of an osteoid osteoma often shows a distinctly zonal pattern with central maturation to thicker, more highly mineralized woven bone. Except for this tendency toward central maturation, the osseous tissue in an osteoid osteoma has osteoid and woven bone at a relatively uniform

stage of maturation in any given lesion. In contrast, osteoblastomas typically display considerable variation in the thickness and degree of calcification of the woven osteoid trabeculae.

**Giant Cell Tumor.** As many as 40% of giant cell tumors will produce woven bone. Distinction from osteoblastoma is important because giant cell tumor is a more aggressive neoplasm. Giant cell tumors of the long bones almost invariably involve the epiphysis, whereas osteoblastomas are rare at this site (13). Giant cell tumors are uncommon in the vertebrae and, when present, almost always arise in the body. Vertebral osteoblastomas favor the arch and processes. In osteoblastoma, the giant cells are smaller, have fewer nuclei, and many represent true osteoclasts that pepper the surfaces of the osteoid and woven bone. Osteoblastoma does not contain the large zones of giant cells and mononuclear stromal cells that are diagnostic of giant cell tumor.

**Aneurysmal Bone Cyst.** Osteoblastoma and aneurysmal bone cyst have clinical and radiographic similarities (13). Furthermore, as mentioned above, osteoblastomas may have a secondary aneurysmal bone cyst component. Marsh, et al. noted such components in 4 of their 25 osteoblastomas (13). Both lesions often involve the spine and, occasionally, they may be confused radiographically. Aneurysmal bone cyst is highly unlikely to be misdiagnosed microscopically as osteoblastoma, but all aneurysmal bone cysts must be carefully examined to exclude the presence of an associated primary lesion such as osteoblastoma.

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## CASE #6

**Malignant Fibrous Histiocytoma**

Malignant fibrous histiocytoma was separated from other soft tissue neoplasms during the early 1960s, and the first description of primary osseous MFH appeared in the radiology literature in 1972. Many of the cases reported since then have been identified in retrospective reviews of tumors originally classified as osteosarcomas, fibrosarcomas, or unclassified sarcomas. MFH is rare, compared with other sarcomas. Dahlin and associates found 35 cases of MFH from a review of 962 osteosarcomas and 158 fibrosarcomas.[4] Spanier and colleagues reviewed "approximately 400 primary tumors" and reclassified eight of them as MFH.[16] A retrospective study of over 1,500 primary tumors at the Rizzoli Institute yielded 42 cases.[2]

The dense collagen that is focally present in MFH is indistinguishable from the collagen of osteosarcoma. In the latter situation this is referred to as osteoid or "malignant osteoid." The term "malignant osteoid" is obviously an erroneous appellation, but it is a shorthand method of saying that the osteoid is thought to be produced by the adjacent malignant cells. This of course forms the basis for the diagnosis of osteosarcoma. The question is: When is collagen osteoid rather than mere collagen? This cannot be answered with certainty unless the collagen has become mineralized and thus has become bone. There is a clue, however, if the osteoid has a complex filigree interlacing pattern. In MFH, there may be small foci with this appearance, but for the most part, the collagen is either present as long bands, broadly hyalinized areas, or arranged in a storiform pattern. To be sure, all of these can be seen focally in osteosarcoma, but unless there are areas of the clear-cut filigree pattern, osteosarcoma can be eliminated.

Most authors noted that some of their cases of osseous MFH had small areas of "true" osteoid. Nonetheless, in the enthusiasm for this new entity, there was general agreement that small areas of osteoid were acceptable, and that they did not deter one from the diagnosis of MFH. One authority, however, excluded a tumor from MFH even if there was a "single microscopic focus of osteoid."[10] The lower limits of allowable osteoid in MFH has never been defined. In the past, the distinction between OS and MFH was believed to have clinical relevance because of the seemingly better prognosis of MFH. Currently, however, OS and osseous MFH are believed to have similar biologic behaviors, rendering the distinction of no clinical significance. There is sufficient evidence that these predominantly non-osteoblastic neoplasms belong in the spectrum of OS, even if there is only focal osteoid production.[6] There is also preliminary evidence that MFH of bone responds to the chemotherapeutic regimens that are effective for OS.[1,19]

**Radiologic Appearances.** The roentgenographic appearance of MFH is usually that of a radiolucent defect with ill-defined margins. MFH is most commonly located in the metaphysis, but it may involve the epiphysis and can extend into the joint.[16] The cortex is often expanded and frequently permeated by the neoplasm. Unlike other malignant neoplasms, periosteal bone formation is almost always absent unless there has been a fracture. Rarely, there is a sclerotic rim of bone along the periphery of the lesion, suggesting that it is a slowly growing tumor. The metastatic potential of one such tumor, however, was manifest within 2 years.[12] Nonetheless, most patients with a geographic type of bone destruction do well.[17]

Between 10% and 15% of MFHs arise in bones with a previous abnormality, of which Paget's disease is the most common. The second most common abnormality is bone infarct. McCarthy et al. found that 4 of their 35 cases of MFH were in bones with infarcts.[12] The usual cause of infarcts is exposure to hyperbaric conditions.[8] In addition, Mirra and associates reported an MFH in a 28-year-old man with homozygous-S sickle cell disease and multiple bone infarcts.[13] MFH has occurred in previously normal bones that were in the field of radiation therapy for nonosseous tumors,[2,4] and one MFH arose adjacent to a metal piece inserted for a traumatic fracture 14 years previously.[11]

**Microscopic Findings.** Malignant fibrous histiocytoma has an extraordinarily broad range

of microscopic images. There are great differences in the proportion of fibroblasts and histiocytes, with one or the other element sometimes predominating to the total exclusion of the other. The fibrous component is especially likely to dominate large areas. The storiform pattern of fibrous tissue can be seen in the cellular areas but is more clearly seen in the densely collagenized foci. Some MFH are quite vascular, with branching channels identical to the "staghorn" configuration found in hemangiopericytoma.

The nuclei of fibroblasts are small or markedly elongated and can be densely hyperchromatic or vesicular. There is a moderate degree of pleomorphism, but bizarre nuclei are less common than in histiocytes. The amount of collagen in the fibrous areas may be sparse, or it can be seen as thin or broad deposits between the cells. Individual cells may be surrounded by collagen. Some of these collagenized foci are indistinguishable from osteoid, and they account for the diagnosis of MFH as osteosarcoma in the past.

The histiocytes are mononucleated or multinucleated. The multinucleated giant cells with bland nuclei are probably reactive, especially those cells with an orderly arrangement of nuclei identical to that of a Touton or a Langhans giant cell. Neoplastic cells have nuclei that range from the mildly atypical to the bizarre. One or more prominent nucleoli is the rule, and occasionally there is clearing of the perinuclear chromatin so that multilobated nuclei resemble, or are indistinguishable from, Reed-Sternberg cells. Phagocytic debris may be seen.

## DIFFERENTIAL DIAGNOSIS

There is one major caveat regarding the diagnosis of osseous MFH. Osseous metastases composed of spindle cells, with or without epithelioid-like neoplastic cells, can pose tremendous diagnostic difficulty. The differential diagnosis includes a variety of metastatic tumors as well as primary osseous sarcomas such as malignant fibrous histiocytoma, leiomyosarcoma, and fibrosarcoma. Spindle cell (sarcomatoid) carcinomas have been reported to arise in the skin, upper aerodigestive tract, and virtually every visceral organ.[22] In particular, osseous metastases from spindle cell (sarcomatoid) renal cell carcinomas commonly involve bone and may closely mimic malignant fibrous histiocytoma. Immunohistochemistry is of major importance in distinguishing between these two lesions. Proper decalcification has not been shown to significantly alter the intensity or sensitivity of immunohistochemical staining.[14] It must be remembered, however, that some antigens are shared by both carcinomas and sarcomas. Vimentin, almost invariably present in sarcomas, may be synthesized by carcinomas and malignant melanoma. Cytokeratin, present in most carcinomas, has been reported to occur in skeletal leiomyosarcoma[15] and other mesenchymal neoplasms including MFH.[21] A useful diagnostic immunohistochemical panel for spindle cell lesions includes cytokeratin, epithelial membrane antigen, S-100, vimentin, desmin, and muscle specific actin. The presence of epithelial membrane antigen or keratin strongly suggests the diagnosis of metastatic carcinoma. Diffuse S-100 positivity suggests a malignant melanoma, given the appropriate light microscopic appearance, and this can be confirmed by staining with the melanocytic marker, HMB-45.

If the cytokeratin, epithelial membrane antigen, and S-100 stains are negative, the differential diagnosis then lies among different primary sarcomas (and rarely, metastatic leiomyosarcoma). Vimentin stains some cells in malignant fibrous histiocytoma and fibrosarcoma, and may be present in leiomyosarcoma. The latter, however, strongly stains with muscle specific actin, desmin, and smooth muscle actin. Fornasier and Paley[7] found 10 reported cases of metastatic leiomyosarcoma, mostly from the uterus, initially presenting as a skeletal metastasis. The metastases were often to osseous sites that are uncommon for primary leiomyosarcoma such as the skull, spine, and scapula.

Some well-documented primary skeletal leiomyosarcomas were initially diagnosed as fibrosarcomas or malignant fibrous histiocytomas.[15] Fibrosarcomas have a more distinct fascicular pattern with sharply delimited fascicles resulting in a herring-bone arrangement. Leiomyosarcoma shares with

malignant fibrous histiocytoma foci of storiform architecture, as well as scattered giant cells. Immunostaining for muscle specific actin or desmin distinguishes leiomyosarcoma from fibrosarcoma and malignant fibrous histiocytoma. The presence of occasional cytokeratin positivity in leiomyosarcomas mandates the use of a panel of immunohistochemical markers. In the event of equivocal immunohistochemical stains, electron microscopy may aid in differentiating epithelial cells from smooth muscle.

Malignant fibrous histiocytoma is the usual component of so-called "dedifferentiated chondrosarcoma." It has been well shown that this is of a different lineage and does not constitute dedifferentiation.[23] The MFH metastasizes in the absence of the cartilage. The cartilage is almost invariably low grade; representing either an enchondroma or a grade I chondrosarcoma. The MFH constituent is at the periphery of the lesion and is easily encountered as the first abnormal tissue on a biopsy. It will occasionally infiltrate between the cartilage, but often abuts it and may be removed as the only tissue. This emphasizes the importance of knowing the radiographic findings. It appears that MFH arising in a cartilaginous neoplasm has a worse prognosis than MFH arising *de novo*. There are virtually no survivors of dedifferentiated chondrosarcoma in the pre-chemotherapy era, whereas approximately 10-20% survive with amputation of *de novo* MFH.

**Prognosis.** It appears that patients with low-grade MFH have a better prognosis than those with high grade tumors. Unfortunately, very few neoplasms are low-grade. Capanna et al. found only 3 of 90 patients with low-grade lesions.[2] Two of these were alive 3.5 and 36 years after surgical treatment. The third patient had a local recurrence 15 months after initial surgery but did not die with widespread metastases until 16 years later. Dahlin et al. found that 2 of 35 lesions were low-grade.[4] One patient was a 6-year-old with a sacral tumor treated by excision and radiation who was lost to follow-up 2 years later but who had evidence of recurrence. The other patient had a tumor of the frontal bone with two recurrences within 4 months. After excision and radiation for each recurrence, the patient remained disease-free for 18 years. Not all long-term survivors have a low-grade tumor. Except for the one patient just mentioned, the remaining long-term survivors in the series of Dahlin et al. had no correlation between tumor grade and prognosis.[18] In another study, the presence or absence of osteoid-like matrix did not correlate with survival.[12] Neither the bone of origin nor the age of the patient are related to prognosis. However, Capanna et al. found that the survival rates for patients with MFH arising in pre-existing osseous abnormalities were significantly lower than survival rates of patients whose MFH arose in normal bone (22% vs 50%).[2] Although early reports suggested that MFH had a better prognosis than osteosarcoma, the accrual of more cases with longer follow-up shows that long-term survival is about 18% for patients treated by surgery alone.[3] One survivor developed MFH in a second bone.[5] This patient had multiple infarcts, and both tumors arose in an area of infarct.

Adjuvant chemotherapy may benefit patients who have had adequate surgical resections, although in one report, it did not prevent local recurrences.[2] Some patients treated with multiple drugs before resection had no viable-appearing tumor in the resected lesion.[5,20] Nonetheless, the role of adjuvant therapy for MFH remains to be more precisely determined, just as it does for osteosarcoma.

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## CASE #7

**Solid Aneurysmal Bone Cyst**

This case presents an interesting problem because of the histologic appearances that can be seen in several lesions. The tissue available for your study has three major patterns. One is a broad area of sparsely cellular fibrous tissue occasionally containing a multinucleated giant cell. This is, of course, not diagnostic of anything. The second is a richly cellular component with numerous multinucleated giant cells that are set in a background of loose fibrous tissue. Within this fibrous tissue are histiocytes, lymphocytes, and a rare neutrophil. Small foci of osteoid are formed as well. In a few foci the mononuclear histiocytes are the predominant feature and such cells would be identical to what might be seen in a giant cell tumor. The third major component consists of vascular spaces of varying size. Some of these are lined by giant cells and fibroblasts; none has a flattened layer suggesting endothelium.

The earliest change in the vascular component appears to be hemorrhage within the fibrous areas or the giant cell-rich areas. This extravasated blood is then seen to surround blood vessels which are presumably pre-existing normal blood vessels. However, there are vascular channels that are gigantic and far exceed the size of normal vessels in the sense that there is no vascular wall of proportional thickness. These spaces lack an endothelial lining. They are typical of the vascular channels that are seen in aneurysmal bone cyst.

### DIFFERENTIAL DIAGNOSIS

Several craniofacial osseous lesions have giant cells set in a loosely fibrous stroma as seen in your case. To recapitulate the findings of the solid areas described above, the vascularity includes normal vessels but also unusual vascular channels the size of small to moderately large arteries and veins. However, they lack a muscular wall. These channels are rarely lined completely by flat cells that look like endothelial cells. They more often have a mixture of flat fibroblast-like cells and giant cells or are lined by giant cells alone. Extravasation of erythrocytes into the stroma is conspicuous. Multinucleated giant cells sometimes are clustered in the areas of extravasation.

The above constellation of findings is found in giant cell granuloma, the solid component of aneurysmal bone cyst, brown tumor of hyperparathyroidism, and cherubism. No group of clinically diverse lesions more clearly illustrates that there are only a finite number of cells that can proliferate in totally unrelated diseases, and there are only a limited number of patterns that they can take.

Giant cell granuloma, brown tumor, and cherubism are completely indistinguishable microscopically; it is the clinical findings that establish the diagnosis. Cherubism is a familial condition of childhood with massive enlargement of the mandible of the maxillae. Solitary brown tumor of the jaw may be the presenting lesion of hyperparathyroidism.[12] It is only after these conditions have been excluded that giant cell granuloma becomes an acceptable diagnosis.

If one concentrates on the vascular areas of this lesion, a strong case can be made for the interpretation of aneurysmal bone cyst (ABC). There are fibrous septa separating vascular spaces of varying size. As stated above, the vascular channels are not lined by endothelial cells but, rather, cells that look like histiocytes, fibroblasts or multinucleated giant cells. Moreover, there are some strands of osteoid that have formed in these septa. This is a common feature of ABC. It becomes of diagnostic importance when the trabeculae are wavy or bent as the septum assumes an irregular shape. The osteoid rarely mineralizes, therefore it is flexible and this serpiginous configuration is diagnostic of ABC even when it is seen only on a small biopsy. Obviously, it does not rule out an underlying lesion, but identifies an ABC component. The diagnosis of ABC is not mitigated by the more solid areas that are typical of giant cell granuloma (GCG).

As already mentioned, aneurysmal bone cyst (ABC) has fields identical to giant cell granuloma (GCG). The distribution of ABC within the craniofacial bones is the same as GRG. Roughly 60% are in the mandible, 35% are in the maxilla, and the rest are in the cranial bones.[8,11,14,18,21] Interestingly, an ABC of the ethmoid[1] and one in the sphenoid[6] arose during pregnancy. Another patient with a rapidly enlarging lesion in pregnancy was diagnosed as

having giant cell granuloma.[9] The latter is probably better interpreted in retrospect as solid aneurysmal bone cyst (*vide infra*).

The vascularity of GCG often includes some closely approximated vascular channels separated by narrow bands of stroma. When lined by giant cells, these foci are, in effect, miniature ABC. Struthers and Shear have suggested that these channels (which they call "microcysts") are indeed the forerunner of ABC.[16,17] Depending on one's threshold for the diagnosis of ABC, the distinction between GCG with many microcysts and ABC with broad septa is arbitrary. As with ABC in any location, the possibility of an underlying lesion such as fibrous dysplasia must be considered.

**Solid Variant of ABC.** This entire problem is accentuated by the recent introduction of the rubric "solid variant of aneurysmal bone cyst." The term is derived from lesions having a fibro-giant cell background with a minimal vascular component. Sanerkin et al., who coined this term, reported four cases, one of which involved the ethmoid and orbit in a 5-year-old.[15] Solid aneurysmal bone cyst has gained a foothold in the literature.[2,20] In two series from the Rizzoli Institute and Mayo Clinic respectively, the frequency of solid ABC was 7.5% and 3.4% of "classic" ABC. Excluding the small bones of the hands and the craniofacial bones, the distribution in long bones and radiologic features were not different. Follow-up was provided only in one series and none of 15 cases had recurrence.[2] From a histologic standpoint, there has been a great deal written and a great deal poorly illustrated on "chondroid aura." This was noted in nine of the 15 cases from the Rizzoli Institute and five of the eight cases from the Mayo Clinic. This was variously described as calcified cartilage matrix, calcified osteoid, and calcified myxoid tissue of no further differentiation.

The issue of defining the solid variant has brought many to realize that it is perhaps nothing more than a giant cell granuloma. This was the conclusion of Dr. Hubert Sissons in 1986 at the closed session of the International Skeletal Society and also the opinion of Dr. Howard Dorfman at the closed session of the International Skeletal Society in 1988. (Unpublished minutes of the meetings)

**Giant Cell Tumor.** One neoplasm that momentarily enters into the differential diagnosis of GCG is giant cell tumor (GCT). GCT is diagnosed by the presence of sheets of mononuclear histiocytes, which accompany the giant cells. Qualitatively, the mononuclear cells scattered in the fibrous stroma of GCG are indistinguishable, but sparsely scattered. The greater quantity of monocytes forming sheets of the mononuclear cells in GCT distinguishes the two.

Does GCT ever involve the craniofacial bones? A review of 546 cases of giant tumor treated at the Mayo Clinic yielded 15 cases; 11 of which were in the sphenoid bone.[3] Their descriptive criteria and illustrations are diagnostic of GCT. The fact that there are so few reported craniofacial GCT reinforces the caution with which the diagnosis should be made. The importance of recognizing a true GCT is because of its local aggressiveness, which exceeds the usual ABC or GCG. Four of the patients were dead of disease due to uncontrolled local growth and four others were alive with tumor but with major neurologic abnormalities including blindness.

Approximately 20 patients with Paget's disease of the skull or facial bones have had tumors diagnosed as GCT. Upchurch et al. reviewed several of these cases and concluded that they more closely resembled GCG.[19] Only one of the cases in the Mayo Clinic series described above was a GCT arising in Paget's disease.

**Clinical Relevance of Gnathic ABC vs. GCG.** From a practical standpoint, there will not be any initial management difference whether the diagnosis is ABC or GCG. The lesion will be curetted. In a compilation of the literature, there are no major differences between ABC and GCG.[10] Both have an age range from 5 to 70 years of age. At least 90% of ABC occur in patients less than 30 years of age and 75% of GCG are less than 30 years old. In both groups, teenagers form the peak decade. There is no difference in gender preference; females outnumber males two to one in both groups. GCG is slightly more common in the mandible

(2:1) than ABC (3:2). Lesions that have been diagnosed as ABC do have a higher recurrence rate of approximately 25%. The recurrence rate for GCG is in the range of 10-20%.

**Problematic Cases that Rarely Get Published.** The exact classification of lesions with the congeries found in this case can be arbitrary. Naturally, there is a preference for authors to write about cases in which they have made a diagnosis. Similarly, editors may not be open minded to cases in which there is no "clean" diagnosis. Occasionally, courageous authors and equally courageous editors will publish papers that discuss problems without arriving at a specific diagnosis. A good example of this healthy phenomenon was published by de Mello et al.[7] They described a 4-year-old with tumorous involvement of the facial bones by fibrous tissue, giant cells, and new bone formation.[7] Slides from their case were seen by a number of pathologists experienced in bone lesions. They generated a spectrum of diagnoses that included "giant cell lesion," "aneurysmal bone cyst with large areas of giant-cell reparative granuloma," "benign fibro-osseous lesion, not further classified," and "well-differentiated osteosarcoma." In a paper illustrating similar images in the sacrum, Dehner et al. acknowledged that their cases "represent a nosologic enigma" and gave them only a descriptive diagnosis.[5] These are commendable publications that bring the many uncertainties of fibro-giant cell lesions into the open and sometimes stimulate further published dialogue.[4,13]

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## CASE #8

### Pigmented Villonodular Synovitis

Pigmented villonodular synovitis (PVNS) is a fibrohistiocytic proliferation producing innumerable villous and nodular synovial protrusions. Large quantities of hemosiderin result in a brown or tan color.

Pigmented villonodular synovitis and localized nodular synovitis (LNS) are often viewed as variants of the same disease. When the entire synovium is involved and there is a major villous component, the process is interpreted as pigmented villonodular synovitis. The presence of more solid, nodular masses in an otherwise predominantly villous, diffuse synovitis indicates that PVNS and LNS overlap both grossly and microscopically. The clefts that are seen in solid areas of some cases of localized nodular synovitis are probably remnants of spaces between fused villi. Despite these similarities, the prognostic differences between the two lesions warrant their separation.

The cause or causes of pigmented villonodular synovitis or localized nodular synovitis are unknown. Some authors view them as benign neoplasms, and one case with trisomy 7 supports this concept.[17] Most pathologists, however, interpret these as reactive. As with almost all diseases of uncertain cause, an autoimmune pathogenesis has been suggested.[1] It is of interest that both diffuse and localized forms of synovitis have been reported in several patients with rheumatoid arthritis.[18] Some (if not all) cases of PVNS diagnosed in patients with rheumatoid arthritis actually represent a reactive synovial proliferation. The association of pigmented villonodular synovitis with hemangioma in children raises the possibility that repeated hemorrhage from an underlying vascular malformation could be a cause.[2] Hemorrhage alone probably does not account for the lesion, however, because the joint changes in hemophilia differ from those of pigmented villonodular synovitis.

There is a preponderance of females with the ratio reaching as high as 2:1. Patients range from 4 to 60 years of age, with most in their third or fourth decade of life. Complaints include pain, often accompanied by intermittent or steadily progressive swelling. There is often a progressive limitation of motion. Symptoms range in duration from six months to 25 years, with an average of six years. Two-thirds have a bloody effusion.

More than 80% of reported cases of PVNS have involved the knee. The hip joint accounts for about 15% of cases, with a few examples reported in the ankle, foot or hand, elbow, and shoulder. Rare patients have had multiple joint involvement, which tends to be bilateral and symmetrical.[5,21]

**Radiographic Bone Destruction.** Approximately 25% of PVNS lesions in the knee invade bone, and 80% of the cases that occur in other joints such as the hip, shoulder, and ankle will have bone involvement.[7] PVNS can infiltrate into muscle,[6] and one case was controlled only by amputation.[14] Bone involvement by PVNS can mimic a primary neoplasm of bone when it involves only one side of the joint.[12] These contain myxoid material, fluid, or are infiltrated by the synovium with all the features of villonodular synovitis. The cysts are usually present in bones on both sides of the affected joint. Rarely, only a single bone may be involved and the appearance mimics a primary osseous neoplasm.[12] Computed tomography demonstrates the extent of the disease. It is particularly useful in locating recurrent lesions and demonstrating that popliteal and posterior calf soft-tissue masses are due to extensions from the knee joint itself.[3]

**Gross and Microscopic Appearance.** Grossly, the synovium is light to dark brown with small yellow foci. It is usually diffusely involved, although small patches of normal synovium can remain. Occasionally, only a few square centimeters of synovium are affected. The villous projections are variable in size and shape and number in the hundreds or thousands. They may be filamentous, plump, or beaded. In addition, there are often broad nodules, either forming flat pads on the synovium or polypoid projections above the surface. Articular cartilage can be eroded by lesional tissue,[16] and there may be extension into adjacent muscle.[6] In one case involving the hip, the femoral head was invaded via the insertion of the ligamentum teres.[8]

Microscopically, the villi are covered by reactive-appearing synovial cells containing abundant hemosiderin. The synovial layer merges imperceptibly into the underlying cellular infiltrate occupying the central core of the villi or nodules. Hemosiderin is also within macrophages or lies free in the stroma. Foamy histiocytes are common, and multinucleated giant cells are always seen. Broad areas of fibrosis can be present, and some villi have densely fibrotic or sclerotic cores. The solid nodules focally contain clefts lined by apparent synovial cells. Lymphocytes may be present in the stroma, but they rarely are prominent, and other inflammatory cells are notably absent. Mitotic figures are usually easy to find in the synovial and stromal cells, and may be numerous.

## DIFFERENTIAL DIAGNOSIS

Traumatized synovium may react by the formation of numerous well-formed villi. However, the synovium maintains its pink or light tan color and lacks the darker color of PVNS. Microscopically, the reactive synovium lacks the foam cells, giant cells, and hemosiderin that are conspicuous in PVNS. Joints involved with rheumatoid arthritis may also have villi, but these usually contain many plasma cells and lack conspicuous hemosiderin.

Intraarticular hemorrhage in hemophiliacs can elicit a villous change with large deposits of hemosiderin confined to the synovial lining cells. The subsynovial tissue, in contrast to pigmented villonodular synovitis, is almost totally devoid of hemosiderin. The villous change is seen only in the early stages of chronic hemarthrosis, because later stages result in a flattened synovium with underlying fibrosis.[19]

Villonodular hyperplasia may also occur in joints that have been replaced with prostheses (*vide infra*). The identification of foreign material easily distinguishes this *detritic synovitis* from pigmented villonodular synovitis.

A few cases of diffuse synovial neoplasms with local bone invasion and distant metastases have been reported.[15] Their exact classification and relation, if any, to pigmented villonodular synovitis are unclear.

Intra-articular localized nodular synovitis may have synovial-lined clefts and resemble a biphasic synovial sarcoma. However, the cells in localized nodular synovitis are not clearly epithelial, gland-making cells. Instead, they have the appearance of histiocytes.

**Prognosis.** Pigmented villonodular synovitis is difficult to eradicate, except in rare cases where it is localized to a portion of the synovium that can be completely excised with wide margins. Localized surgical excision is followed by recurrent symptoms in 21 to 46% of cases.[10] Spontaneous regression is rare.[11] An occasional case with extensive, destructive local growth may require amputation.[14] Some patients require hemiarthroplasty, total arthroplasty, or arthrodesis when there is severe joint destruction.[20] Symptoms may be relieved with external beam radiation or the intraarticular instillation of radiocolloid.[22]

It is apparent that there are major clinical differences between localized nodular synovitis (LNS) and diffuse PVNS. Even if these are simply quantitatively different expressions of the same disorder, it is mandatory to separate them in terms of the prognostic implications. Bone invasion and joint destruction do not occur with LNS. As one might expect, segmental excision of synovium will invariably cure LNS,[9] whereas diffuse PVNS requires extensive synovectomy with its attendant morbidity.

Malignant tumors arising in LNS have been sporadically reported.[4,13] The cytologically malignant component, which resembles either malignant fibrous histiocytoma or clear cell sarcoma, is accompanied by a blander component of mononuclear cells and giant cells. Whether these represent, in the case of malignant fibrous histiocytoma, an extremely well-differentiated part of the neoplasm or a pre-existing LNS is a moot point. In the case of clear cell sarcoma, the possibility that the mononuclear cells and the giant cells are only reactive cannot be discounted. Certainly no lesion with the typical features of LNS has metastasized.

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**Detritic Synovitis**

Approximately 300,000 to 400,000 total joint replacements are inserted each year worldwide.[8]

Prosthetic materials fall into three major categories: metals, polymers, and methyl methacrylate, which is the cement used as a filler between the prosthesis and bone. Most of the metals are alloys consisting mainly of chromium and cobalt, with smaller quantities of other metals. The polymers include polyethylene, silicone elastomer, and proplast, which is a polymer of Teflon and carbon. All of these substances have a distinctive appearance in histologic sections.

Metallic devices rapidly wear so the synovium is gray or black within a few months. Microscopically, metallic debris is a black powder lying free in fibrous tissue or within macrophages. The material is birefringent and may range from tiny round grains to small rectangular rods up to 4 microns long.

The polymers that are abraded by articulation evoke a greater histiocytic response than does metal dust. Silicone particles are faintly yellow, have a nodular configuration, and measure up to 75 microns in diameter. They are faintly luminescent but not birefringent under polarized light. Polyethylene particles appear as almost colorless shreds of various shapes and sizes, and they are strongly birefringent.[6]

Methyl methacrylate is totally, or almost totally, dissolved away during tissue processing. The histiocytes that contained the cement have a large, almost completely clear vacuole; and clear holes can also be found in the stroma.[3] The microscopic footprint for methyl methacrylate is barium sulfate, which is sometimes mixed with the cement to make it radiographically visible. The barium has the golden, finely granular appearance that all of us have seen on the mucosa of the colon or in the appendix.

Silicone prostheses also have been associated with severe synovitis that has not only a histiocytic response but also a heavy infiltrate of lymphocytes and, to a lesser extent, plasma cells and eosinophils.[9] The synovial reaction to silicone knee prostheses may be so severe as to contribute to rupture of the patellar tendon.[11] The synovial reaction may necessitate removal of the prosthesis and arthrodesis.[16]

Regional lymphadenopathy is another complication of silicone prostheses. The adenopathy may appear from 5 to 9 years after the insertion of the prosthesis, and it may occur even in the absence of synovitis or malfunction of the prosthesis.[4,5] Inguinal adenopathy occurred in one patient 9 years after insertion of a hip prosthesis.[14] Recently, sinus histiocytosis due to the accumulation of cobalt-chromium and titanium has been described.[1]

Aside from the local complications of loosening and synovitis, the long-term systemic effects, if any, are not known. Patients with metal prostheses have elevated levels of cobalt, chromium, molybdenum, and nickel in their blood, urine and hair.[3] Allergic sensitivity to metals and methyl methacrylate has occurred, and it has been suggested that loosened prostheses may be due to local tissue sensitivity with necrosis rather than to mere mechanical failure.[3] Larger quantities of methyl methacrylate have been seen in veins at the termination of hip arthroplasties,[15] and polymer fragments have been found in the lungs of dogs with joint prostheses.[3] A final concern is the carcinogenic effect of the various materials, since all of the substances used in prostheses produce sarcomas when injected into rodents. The relevance of these studies to humans remains to be determined. Thus far, there have been only three cases reported of sarcoma developing at the site of a hip prosthesis. One patient was a 77-year-old woman who developed pain 2 years after a total hip arthroplasty. A biopsy showed malignant fibrous histiocytoma. She refused therapy and was lost to follow-up.[2] Another patient had an osteosarcoma in the femur adjacent to a prosthesis that had been in place for 5 years, and he died without undergoing therapy.[12] The final patient had a malignant fibrous histiocytoma develop 4 years after insertion of the prosthesis.[13] In none of these patients had there been a pre-existing abnormality in the bone receiving the prosthesis, nor did the patients have Paget's disease. Between 1956 and 1980, four sarcomas were reported in sites where metal plates had been inserted for traumatic fracture.[7] Recently, a malignant fibrous histiocytoma that arose at the site of a plate was reported.[10] Even if there is a direct cause-and-effect relation in some of these

cases, they attest to the rarity of neoplasms associated with prostheses.

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### Intra-Articular Synovial Sarcoma

Intra-articular synovial sarcomas have been the subject of an abstract publication of six cases[1] and two case reports.[2,3] Patients have ranged from 9 to 49 years of age. Presenting symptoms relate to internal joint derangement[1] and, occasionally, effusion.[3] All examples of intra-articular synovial sarcoma have involved the knee, except for a single case arising in the elbow.[1]

Typically, there is a well-defined, polypoid mass with a small point of attachment to the surrounding joint capsule. Alternately, there may be diffuse involvement of the synovial surface.[3]

Six of eight have been biphasic tumors. The two remaining cases had a "predominantly" monophasic, spindle-cell pattern.[1] Immunohistochemical studies, of both intra-articular and soft tissue synovial sarcomas have demonstrated strong cytokeratin and epithelial membrane antigen positivity in the epithelial areas, as well as clear-cut positivity for these markers, along with vimentin, in the spindle cell elements.

Our patient had a polypoid lesion with a small base of attachment to the joint capsule.[2] He was treated by local excision and is alive and well over nine years later. Diffuse synovial involvement may require ablation of the limb. In one case with diffuse synovial involvement, pulmonary metastases were found three months after the initial arthroscopic synovectomy, and the patient died of respiratory failure seven months after initial diagnosis.[3]

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## CASE #9

### Synovial Chondromatosis

Synovial chondromatosis is the formation of multiple, benign cartilaginous nodules in the synovium, many of which become detached and float within the joint space. At least four loose bodies in the absence of degenerative joint disease is the generally accepted criterion. We personally like to adhere to the more stringent definition that requires evidence of a chondromatous alteration in the synovial membrane itself.[8] Synonyms include *synovial osteochondromatosis* and *synovial chondrometaplasia*.

Most authors believe that synovial chondromatosis (SC) is a reactive process of unknown cause rather than neoplastic. Trauma (e.g. professional athletes) does not seem causative.[7] There is good evidence that SC is self-limited and can resolve spontaneously.[14] Patients range from 14 to 67 years of age, with a peak in the fifth decade of life.[17] Males are afflicted twice as often as females. Clinical findings consist of various combinations of pain, swelling, and limited motion for durations of one month to several decades. On the average, patients are symptomatic for about five years.

The knee is the most common site of involvement, accounting for about two-thirds of patients, with the hip and elbow being about equally divided as the next most frequent sites. There have been isolated reports of synovial chondromatosis involving the joints of the shoulder, ankle, carpal and tarsal bones, and mandible. About 10% of the knee, hip, elbow, and shoulder lesions are bilateral and, rarely, three joints may be involved. Two siblings were reported who had bilateral knee disease.[21]

Radiographs are strongly suggestive of the diagnosis if numerous calcified bodies are visualized. However, not all loose bodies are calcified, and in about 10% of patients with synovial chondromatosis no abnormal calcifications are seen.

Grossly, the synovium may be diffusely studded with hundreds of nodules or, less commonly, only a few square centimeters may be affected.[7] The area near the synovial-cartilaginous junction tends to be most heavily involved. The surface has irregular, flat bumps, polypoid nodules of various shapes, and pedunculated masses on long delicate stalks. The individual nodules, whether free or attached, vary in size from less than a millimeter to 3 cm. The loose bodies, which can number over 1200, may have a smooth surface or be granular. The latter finding suggests fusion of smaller nodules.

Extra-articular SC arising in a bursa has been reported to coexist with intra-articular disease. The lack of a connection between the cartilaginous bodies in the joint and the bursa eliminate the possibility of soft tissue invasion from the joint lesion.[20]

Microscopically, the earliest stage of SC is the formation of round, cellular islands of cartilage in the connective tissue of the joint capsule, beneath, but not involving the synovial lining cells. Occasionally, the smallest microscopic foci consist of loosely arranged trabeculae of bone. Most nodules consist only of cartilage, but larger ones, including those protruding above the synovial membrane and lying free in the joint, may also contain well-formed bone with fatty marrow.

Enlarged chondrocytes with pleomorphic nuclei and binucleated cells are found focally in about two-thirds of cases. Free-floating nodules may be covered with a layer of synovium. The cartilaginous component of detached nodules is usually intact, even when there is necrosis of the underlying bone and fatty marrow.

### DIFFERENTIAL DIAGNOSIS

The most important consideration in the differential diagnosis of SC is synovial chondrosarcoma (*vide infra*). Bertoni et al. have identified several microscopic features from cases of metastasizing synovial chondrosarcoma that are indicative of true malignancy.[1] These include: chondrocytes arranged in sheets without a clustering architecture; crowding of cells, especially with spindle cells; myxoid change in the stroma; necrosis; and, on rare occasions, mitotic figures. Extension beyond the joint capsule should heighten the suspicion that the lesion is chondrosarcoma, but some cases of synovial chondromatosis have extra-articular extension.[14]

The differential diagnosis also includes secondary synovial chondrometaplasia that occurs when pieces of bone or articular cartilage

are chipped off into the joint space due to trauma or degenerative joint disease.[16] These fragments become embedded in the synovium and may stimulate a secondary cartilage metaplasia. The nodules differ from synovial chondromatosis by having a concentric layering of cartilage, enchondral ossification, and a lack of nuclear atypia.[22] Patients with synovial chondromatosis may have secondary degenerative joint disease, and therefore, have some nodules with features of secondary synovial chondrometaplasia. Conversely, the diagnosis of synovial chondromatosis can be made in the absence of synovial disease if the loose bodies consist of cartilage and bone lacking the concentric layering.[16]

There have been a few reports of intra-articular osteochondromas.[19] These have been large (up to 5 cm) osteocartilaginous masses attached to the synovium by a pedicle. The surface of the lesion is covered with cartilage and the central portion is bone, in a pattern resembling an osteochondroma. It seems doubtful that these unusual lesions are related to diffuse synovial chondromatosis.

**Prognosis.** SC is usually treated by the removal of loose bodies and the involved synovial membrane. Many authors have pointed out that the disease appears to be self limited, since even in the absence of total synovectomy, recurrence is uncommon.

A few cases of SC have had one to three extra-articular masses of cartilage that were easily shelled out and did not recur.[5,10] In other cases, extra-articular extensions have enlarged, even in the absence of intrasynovial disease.[14]

**Synovial Chondrosarcoma.** Synovial chondrosarcoma, either primary or secondary to synovial chondromatosis, is extremely rare. We have identified 24 reported cases. Patients have ranged from 28 to 70 years of age. Most synovial chondrosarcomas have involved the knee with rare examples in the hip, elbow, or ankle. Fifteen of the 24 patients have been males, suggesting a slight male predominance. Symptoms of pain or swelling have been present for one month to 25 years, and, in most patients, the duration exceeds one year. About half of the reported cases have evidence of concurrent, and presumably pre-existing, synovial chondromatosis.[13] Two patients had biopsy-proven synovial chondromatosis 24 and 25 years prior to developing a synovial chondrosarcoma.[9,15]

Radiographically, intra-articular calcified bodies may be present that are indistinguishable from those of synovial chondromatosis. The major radiographic distinction, if present, is the finding of calcified masses lying not only within the joint space but also extending to involve the surrounding soft tissues.[17] Uncommonly, there is radiographically detectable erosion of an adjacent bone.[1]

Grossly, the joint space contains variable numbers of loose bodies, and the synovium has the nodular appearance of synovial chondromatosis. The diagnostic gross feature, if present, is widespread extension of lobulated cartilaginous masses far beyond the joint capsule and into the surrounding soft tissues[6] or bone.[9] The cartilage may be more mucinous and glistening than that of synovial chondromatosis. In one case, vein invasion was grossly evident.

Microscopically, synovial chondrosarcomas often have a lobular pattern with marked hypercellularity. Spindle cells at the periphery of the lobules were seen in four of 10 cases in one series.[1] The chondrocytes of chondrosarcoma tend to be scattered in sheets and lack the clustered pattern that is usually present in synovial chondromatosis. Myxoid change is often present. In one case, an intrasynovial chondrosarcoma had the characteristic pattern of myxoid chondrosarcoma, as seen in soft tissues.[11] Synovial chondrosarcomas range from grade 1 to grade 3. The diagnosis of grade 1 chondrosarcoma should be made only in conjunction with unequivocal invasion beyond the joint capsule, in order to distinguish it from synovial chondromatosis with prominent nuclear atypia.

Treatment of synovial chondrosarcoma has usually consisted of aggressive surgery in the form of amputation or extra-articular resection with reconstruction. Biopsies should be carefully planned, as poorly done procedures may contaminate tissue planes and necessitate subsequent amputation, rather than reconstruction. Nine of 24 reported patients with synovial chondrosarcoma have developed pulmonary

metastases, usually within 30 months following diagnosis. Follow-up for the remaining patients is short in most instances.

**Soft Tissue Chondroma.** Soft tissue chondromas (STC) occur predominantly in the hands and feet. They may be intimately associated with the synovial lining of tendon sheaths, and thereby may be thought of as a cousin of synovial chondromatosis. Most soft tissue chondromas (80%) occur in the fingers. The hands, toes, feet, and trunk are less frequently involved. STC usually consists of a slowly enlarging nodule or mass. Most patients are between the ages of 30 and 60. Although usually solitary, Dellon et al. described bilateral chondromas in a patient with renal failure.[4] Occasionally there is radiographically demonstrable calcification. The bones are not invaded, but some tumors cause compression deformities.

Grossly, the excised STC is usually a sharply demarcated round or oval tissue that is soft or friable. They rarely exceed 3 cm in greatest dimension, and may be attached to tendon or tendon sheath. About two thirds consist of mature hyaline cartilage with a lobular pattern that may or may not be well defined. There may be broad zones of fibrosis and occasionally ossification. Hemorrhage and myxoid change are occasionally evident. Roughly one third have focal or diffuse calcification that may obscure the cartilaginous elements and mimic tumoral calcinosis. Approximately 15% of cases have a proliferation of giant cells and epithelioid histiocytes at the margins of the nodules.

Hypercellular foci including binucleated cells and cells with nuclear atypia are frequent but do not correlate with recurrence. We are unaware of a case of STC associated with or followed by chondrosarcoma. About 15% of patients have a recurrence.[2,3]

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## CASE #10

**"Transitional" Carcinoma Arising in Inverted Papilloma**

There are several pieces of tissue on the slide. Some of these are ordinary inverted papilloma (IP), and other pieces are from a papillary carcinoma. Each of these components will be described separately. Attention will be directed at the presumably pre-existing inverted papilloma, which is one species of Schneiderian papillomas.

Schneiderian papillomas include fungiform papilloma, inverted papilloma, and oncocytic Schneiderian papilloma. More than 1300 had been reported by 1993.[3] The fungiform and inverted papillomas are lined by the same variety of epithelium. The most common type of epithelium is frequently referred to as transitional because it bears a resemblance to transitional cell epithelium of the urinary tract. It does, however, lack an umbrella layer. Therefore, it is similar in appearance only. Many of us prefer to call this intermediate epithelium; intermediate between the columnar cells of ciliated epithelium and the rounder cells of squamous epithelium. IP may also be lined by squamous epithelium or ciliated epithelium (either of normal thickness or greatly thickened). The ciliated cells may form a single layer on top of intermediate cells or occasionally on top of squamous cells. Mucous cells usually are individually present but sometimes form small clusters. Mitoses are usually sparse, but in some lesions they are numerous. When present, they are predominantly located in the basal or parabasal region, but sometimes occur in the upper half of the epithelium as well. Atypical forms are not seen. Nuclear pleomorphism is present in about 10% of IP, usually as an isolated cell at any depth in the epithelial lining. Occasionally, atypical nuclei form small aggregates in the inner third of the layer. As with lesions elsewhere in the respiratory tract, this change must be distinguished from basal cell hyperplasia in which the cells have a high nuclear/cytoplasmic ratio. Neutrophils are often scattered in the epithelial layer and sometimes are present in large aggregates. This produces a disquieting histologic appearance to the lesion, and there may be mild nuclear atypia in the epithelial cells. Presumably this is inflammatory atypia. Marked inflammatory change has been well described, and it has no correlation with recurrence.

The stroma of all Schneiderian papillomas is either fibrous or edematous and contains blood vessels of varying size. Inflammatory cells can be absent or abundant. When present, plasma cells, lymphocytes and neutrophils are predominant, but eosinophils may be numerous. The inflammation is identical to inflammatory (allergic) polyps. The stroma, however, differs from that of inflammatory polyp by lacking seromucinous glands. Seromucinous glands are present in Schneiderian papillomas only at their base at the site of origin from the mucosa.

Rarely, there are edematous nasal polyps in conjunction with IP. This either represents coincidental inflammatory polyps or is a secondary change due to local physiologic disturbances. There is nothing to suggest that IP is superimposed upon inflammatory nasal polyps or arises as a consequence of that common affliction. Histologically, there are differences such as the inconstancy of inflammation in IP and the sparsity of seromucinous glands in the stroma of IP. Moreover, the epithelial proliferation is much thicker in IP, and transitional epithelium rarely occurs in nasal polyps.

Therapy. In the past, at least 70% of the patients with IP have had recurrences and at least half of this group had two or more recurrences. There are a few months to several years between recurrences and the intervals can be extremely variable, even in the same patient. As a very general statement, recurrences are usually manifest within one year after excision.

In recent years, more aggressive surgery has reduced the recurrence rate to less than 10%.[5] The therapy consists of removal of the medial wall of the antrum which includes the lateral nasal mucosa. The procedure, called medial maxillectomy, requires a lateral rhinotomy, but there is minimal if any cosmetic defect.[5] The bones removed do not contribute to the configuration of the face. Although the initial enthusiasm for medial maxillectomy was great, a more recent report based on 20 patients from the same institution showed that 6 (30%)

had recurrence.[3] It is possible that their more recent cases have more extensive disease and are adversely selected thereby. It is well to keep in mind that clinical bias may result in different therapeutic outcomes. For instance, the recent trend for endoscopic treatment of sinusitis has been applied to the treatment of inverted papillomas. Favorable results have been reported, but the patients may be selected because they have minimal disease.

There have been several attempts to correlate histologic features with the risk for recurrence, but most authors have not succeeded.[18] On the other hand, Snyder and Perzin felt that the presence of atypia rendered patients at increased risk.[21] In their experience, the recurrent tumor usually had even more severe atypia, but sometimes the degree of atypia remained the same and occasionally was less severe. They also found that the presence of mucous cells seemed to be associated with a high rate of recurrence.

**Pathogenesis.** The pathogenesis of IP is unknown. An occasional patient will give a history of allergy or chronic sinusitis, but this is probably not more than the frequency in the population at large. Whether the lesion is infectious or a reaction to noxious inhalants remains to be determined. Epithelial papillomas of the nasal cavity have been produced in hamsters by parenteral and topical introduction of carcinogens, but this information should not yet be extrapolated to humans. HPV 6 and 11 have been found in IP using in situ hybridization.[25] HPV 16 has been found in squamous cancer associated with IP.[23] In another report, HPV 16/18 was found in one case with invasive squamous carcinoma superimposed on IP.[4] It was also seen in a case with only mild dysplasia, but the histologic findings are not well illustrated. Nonetheless, if the diagnosis is considered accurate it raises the possibility that the viruses play a role in the genesis of lesion and possibly in the development of carcinoma. The number of cases studied by in situ hybridization is small, but raise interesting questions. Can infection with HPV 16/18 in the absence of HPV 6/11 result in formation of IP? Does HPV 16/18 infection in IP suggest there may be a greater malignant potential analogous to genital condylomata? On the other hand, can infection with HPV 6/11 alone be associated with dysplasia, or does it require other promoters such as cigarette smoke or pollutants? In the study by Brandwein et al, viral RNA was detected only focally and confined to a few cells in each focus whether in the superbasal or superficial epithelium.[4] Quantitatively, there were fewer copies than are usually seen in condylomas. Moreover, there was no detection of capsid antigen. This suggests that HPV infection of IP rarely results in production of virus in IP, which is consistent with the minimal keratinization seen in IP. This contrasts with the keratinization seen in condyloma or exophytic papillomas that have evidence of capsid antigen virion production.

Judd et al used in situ hybridization on paraffin embedded tissue.[14] All three fungiform papillomas were positive for HPV using three techniques: immunohistochemistry, in situ hybridization for HPV 6/11, and polymerase chain reaction for HPV 11. None of nine inverted papillomas nor three OSP stained with these probes. It is obvious that the role (if any) of papilloma virus in Schneiderian papillomas is, to say the least, not understood.

**Oncocytic Schneiderian Papilloma.** Oncocytic Schneiderian papilloma (OSP) was referred to in the older literature as cylindrical cell papilloma. The pattern of OSP is a serpiginous epithelial proliferation over an edematous or loosely fibrous stroma. There are often invaginations into the substance of the polypoid mass, and the pattern is identical to inverted papilloma. The epithelium is 3 to 6 layers thick and composed of columnar or slightly polygonal cells. The outermost layer may have cilia. The cytoplasm is eosinophilic and finely granular. This is mitochondrial hyperplasia that has been confirmed with electron microscopy.[1]

In addition to the eosinophilic cells, the epithelial layer contains numerous round mucous cells with the nucleus compressed along the edge of the cell. In other foci the mucin appears to be extracellular. Frequently, the mucous deposits contain nuclear debris or neutrophils. Sometimes the mucus is con-

densed as sharply defined droplets that resemble fungal organisms. They must be separated from the organisms of rhinosporidiosis as well as other fungi.

The pathogenesis of OSP is unknown. The epithelial change appears to be a hyperplastic process with some alterations in the columnar cells. The presence of mucous cells and ciliated cells is further support for a hyperplastic process involving multiple cell types.

The rarity of this lesion is reflected by the fact that Hyams had only 10 cases compared to more than 300 cases of inverted papilloma and fungiform papilloma.[13] OSP are undoubtedly included in other published series as examples of inverted papilloma. For example, Fig. 8 in the paper by Snyder and Perzin has the appearance of OSP.[21] As discussed below, the behavior of OSP appears to be identical with inverted papilloma, so that the inclusion of both histologic types under the general heading of Schneiderian papillomatosis is not a serious error.

Oncocytic Schneiderian papillomas occur in adults who are usually beyond the age of 40 years. Patients complain of obstruction, epistaxis, or pain. The distribution, recurrence rate, and association with malignancy parallels that of inverted papilloma.

Although there may be some slight variation in the nuclei of OSP, severe dysplastic changes are not seen. If there are marked cytologic abnormalities, the possibility that the lesion is associated with an invasive carcinoma must be thoroughly investigated. It may require numerous sections to find a small focus of unequivocal invasion. One of the ten cases reported by Hyams was associated with carcinoma,[13] and there are isolated cases reported.[8,24]

**Carcinoma Associated with IP.** As in your study case, inverted papillomas are sometimes associated with malignant neoplasms and this combination often leads to diagnostic problems. It is likely that many inverted papillomas are overdiagnosed as cancer because of cytologic atypia or because IP may erode bone and grow between spicules of bone microscopically. This is not, however, *prime facie* evidence of carcinoma.

The diagnosis of carcinoma should be made only when there is definite invasion by cytologically malignant cells. When the carcinomas are keratinizing squamous cancer, they are easy to diagnose. The problem centers around nonkeratinizing carcinomas. There are three main histologic groups of true IP or IP-like changes associated with cancer.

**Group 1.** The lesion is mostly cancer with a minority of the epithelium looking like IP. These patients rarely have a previous history of IP. Whether the IP-like areas are pre-existing IP or a synchronous mucosal change is unknown. It is also possible that these IP-like foci are extremely well differentiated non-keratinizing carcinoma.[16] For practical purposes (and conceptual purity) these patients should be kept separate from those with histologically clear-cut IP.

**Group 2.** The lesion is predominantly a typical IP but has small areas of either severe nuclear atypia, questionable superficial invasion, or definite invasion by squamous carcinoma (usually). These patients do not develop metastases and rarely have recurrence after radical surgery.

**Group 3.** The entire lesion is carcinoma developing in a patient with one or more prior resections for pure, typical IP. Once there is cancer the course becomes that of cancer occurring *de novo*. Most develop fatal local extension or distant metastases.

Because of different ways of interpreting these groups and the exclusion of some groups in different papers, the frequency of cancer in IP is variably reported. In one study of 39 patients with inverted papilloma there were four cases in Group 1, three cases in Group 2, and one case in Group 3.[10] Thus, about 10% of patients with unequivocal IP (Groups 2 and 3) had carcinoma in some form. Of these groups, patients in Group 3 should be sharply separated since they have a life threatening lesion unlike the patients in Group 2. In combining the many series in which one or more of these groups are identifiable, it appears that about 3% of patients with IP subsequently develop invasive cancer (Group 3), about 3% have small foci of invasive cancer (Group 2), and a number equal to about 8% of

patients with IP are in Group 1.

The carcinomas associated with IP have usually been squamous including one case of spindle cell cancer.[18] A few lesions have had poorly defined lumens and resembled mucoepidermoid carcinomas.[21]

For practical purposes, IP in the absence of carcinoma is not a metastasizing lesion. Two patients have been reported who had involvement by IP in the neck. Whether these represent true metastasis to lymph nodes or a transformation of branchial cleft epithelial remnants is debatable.[10,19]

**Carcinoma of Nose and Paranasal Sinuses.** The classification of malignant tumors of the nose and paranasal sinuses is not well standardized. From a diagnostic standpoint, most lesions are not problems because they are conventional squamous carcinomas with or without prominent keratin. There is a variety, however, of carcinomas that do not lend themselves to a neat classification. These are architecturally papillary but with a considerable mixture of cytologic populations including clear cells.

In effect, papillary carcinomas can include nonkeratinizing squamous carcinoma, keratinizing squamous carcinoma, clear cell carcinoma (with or without a focal squamous component) and transitional cell carcinoma. Some object to the term transitional carcinoma for lesions in this area because the term implies morphologic identity to transitional cell epithelium of the urinary tract. The epithelium of transitional cell carcinoma of nose is different in that it lacks umbrella cells as seen in uroepithelium. Nevertheless, the term transitional carcinoma of the nose is useful because it is a term that has been used in the literature. No better term exists. Secondly, it serves as a reminder of the histologic appearance of this type of epithelium, and one should be alert to the diagnosis of cancer in the nose or paranasal sinuses if the tumor looks like transitional cell carcinoma of the urinary tract.

**Transitional Carcinoma.** The malignant component has a papillary configuration as well as tangentially sectioned "invaginations". The epithelium forms a fairly uniform band of cells overlying the stroma. At low power, the architecture with the uniformly thick layer of cells is indistinguishable from IP. Transitional carcinoma has epithelium similar to the intermediate epithelium of inverted papilloma.[17]

The clinical presentation of transitional carcinoma may be indistinguishable from Schneiderian papilloma including localized bony destruction by radiologic examination. The radiographic destruction may involve the maxillary antrum especially the medial wall, ethmoid sinuses, and occasionally frontal and sphenoid sinuses. Schneiderian papillomas may erode the lamina papyracea to involve the orbit, or extend through the ethmoid sinuses to expose the dura. Radiographic changes often reflect a slow growing process. There may be a fairly sharply circumscribed junction between the destroyed bone and the host bone. This evidence of a slow growing process is common to both Schneiderian papillomas and papillary carcinoma. At the time of surgery, transitional cancer has a corrugated mucosal surface to the surgeon's eye, and it appears identical to Schneiderian papillomas. The consistency of the carcinoma is the same as Schneiderian papillomas. It is not the extremely dense or firm tissue of ordinary squamous carcinoma, which usually has a dense desmoplastic response. The loose stroma of transitional carcinoma and the delicate epithelial lining makes the consistency of transitional cancer softer. Therefore, if the clinician thinks that the lesion is a Schneiderian papilloma and puts this on the pathology requisition card, the pathologist may overlook carcinoma at low power and confirm the clinical diagnosis. It is only when there are either subsequent lymph node or pulmonary metastases that the true nature of the lesion becomes clear. Local recurrence, of course, can be seen both in Schneiderian papillomas and carcinoma, and therefore is not a discriminator.

Transitional carcinomas of the nose and paranasal sinuses are frequently underinterpreted as Schneiderian papilloma. The difference lies only in the cytological population of cells. The nuclear pleomorphism and hyperchromatism of papillary carcinoma distinguish the cells from Schneiderian papilloma.

Friedman and Osborn have updated their material regarding the five year survival of carcinoma of the nose.[12] Squamous carcinoma NOS has a 53% survival in the nose, 14% in sinuses, and 10% "cure rate." The comparable numbers for transitional cell carcinoma are 60%, 40%, and 37.5% respectively. It should be noted, that this does not take into account staging, and the numbers are such that the biologic behavior of papillary carcinoma (transitional type) is uncertain stage by stage (at least as far as I know).

Carcinomas arising in Schneiderian papillomas are uncommonly papillary. Instead, most are conventional squamous carcinomas[2,9,11] although a variety of other tumors such as mucoepidermoid carcinoma, clear cell carcinoma, and spindle cell carcinoma have been reported. On occasion, however, inverted papilloma will be associated with papillary carcinoma. The carcinoma has a markedly different or subtly different cytologic population of cells even if the architecture remains the same. Carcinomas arise in OSP with about the same frequency as they do in inverted papilloma.[6,13,15]

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## CASE #11

**History.** A 62-year-old man presented with a mass involving the region of his right tonsil. A local excision and radical neck dissection were performed.

**Diagnosis. Intestinal-type adenocarcinoma (ITAC).** As discussed below, tumors of this type far more frequently arise in the sinonasal region. Intestinal-type nasopharyngeal adenocarcinomas are distinctly rare.

**Microscopic Features.** Intestinal-type adenocarcinomas of the head and neck region (primarily the paranasal sinuses) display a wide spectrum of microscopic appearances. The current case consists of an obviously gland-forming adenocarcinoma which very closely mimics the microscopic appearance of a conventional primary colonic adenocarcinoma. As discussed below, this is the most common pattern. The range of microscopic appearances for these ENT tumors includes neoplasms which, amazingly, recapitulate normal intestinal mucosa at one end of the spectrum, as well as high-grade, signet-ring adenocarcinomas at the opposite extreme.

Extremely well differentiated forms of intestinal-type adenocarcinoma are often composed of a mixture of papillary, villiform, and glandular elements lined by a heterogeneous population of columnar cells. On H&E section, identifiable types may include cells with single large cytoplasmic vacuoles, columnar cells with homogeneous eosinophilic cytoplasm and a refractile lumenal border, and cells containing coarse, brightly eosinophilic cytoplasmic granules. The coarsely granular cells are Paneth cells, and they stain bright red with a trichrome stain. In addition, this stain may focally reveal a layer of smooth muscle present beneath the more well-formed villous-like structures. Argentaffin and argyrophil stains will often show abundant, basally oriented, spindled cells with numerous granules, representing Kultchitsky-like cells. In the more well-differentiated areas, the pattern may be unrecognizable as a neoplasm and perfectly recapitulate the histology of the normal small or large intestine, complete with a muscularis mucosae (12,16). Although it is tempting to label such proliferations as benign heterotopias, they are highly aggressive, invasive lesions (16).

Another relatively common pattern is one of elongated papillary fronds lined by stratified columnar and goblet cells reminiscent of an intestinal villous or tubular adenoma. Papillary tumors may be invasive, or intramucosal (3,5) Although they may fall short of morphologic criteria for colonic adenocarcinoma, these papillary tumors are also locally aggressive and frequently fatal.

The most common form of intestinal-type adenocarcinoma, typified by the current case, resembles conventional colonic adenocarcinoma. In this variant, glands lined by more pleomorphic columnar cells are often back-to-back, vary in size, and invade the underlying stroma. Intracellular mucin is present focally, but goblet cells are not prominent (3,5). In less differentiated tumors, solid sheets of tumor cells may be present with only scattered glandular lumina (3). Completing the analogy to intestinal neoplasms are the less frequent mucinous tumors that are identical to signet-ring intestinal carcinomas (3,5). The predominant pattern in this variant consists of large glands distended with mucin or pools of extracellular mucin containing small clusters of neoplastic cells. Signet-ring cells form a minor component or, rarely, predominate (5).

**Electron Microscopy.** The resemblance of intestinal-type adenocarcinoma to normal and neoplastic intestinal epithelium is not limited to the light microscopic level. Ultrastructural studies have confirmed the presence of resorptive, goblet, Paneth, and argentaffin cells identical to their intestinal counterparts (1,4,18), and intestinal-type hormones have been documented immunocytochemically (4). The rare intestinal-type adenocarcinoma resembling normal intestinal mucosa and the papillary form resembling villous adenoma can easily be recognized as primary nasal lesions. Intestinal epithelium with this histology is not capable of metastasis. In a review of 82 tumors metastatic to the nose and paranasal sinuses, 5 were primary in the gastrointestinal tract and in some patients the sinonasal lesion was the initial clinical manifestation (6).

**Immunohistchemistry.** Immunocytochemical markers are of limited value to distingulsh nasal tumors resembling conventional or mucinous adenocarcinoma from a metastasis. We determined the immunohistochemical staining profile of 12 sinonasal ITAC and compared their staining with that of 12 histologically similar colonic adenocarcinomas (15). All ITAC stained for cytokeratin and epithelial membrane antigen. Additional positive reactions were as follows: B72.3 - 11 of 12

cases, Ber EP4 - 11 of 12, Leu M1 - 8 of 12, HMFG-2 - 12 of 12, BRST-1 - weak staining in 7 of 12. All 12 ITAC were negative for vimentin, synaptophysin and actin. Colonic carcinomas stained similarly for these markers. Three additional antigens differed in their expression in ITAC versus colonic tumors. Carcinoembryonic antigen (CEA) was strongly present in only 2 of 12 ITAC, with focal positivity in 6 of 12 and no staining in 4 of 12 cases. In contrast, all 12 colonic adenocarcinomas were strongly positive for CEA. Chromogranin-positive cells were present and often numerous in 9 of 12 ITAC, in contrast to only rare positive cells in 3 of 12 colonic tumors. Neuron specific enolase was present in 5 of 12 ITAC, but was absent from all colonic tumors studied. ITAC are less often and less strongly CEA positive and more prone to exhibit divergent neuroendocrine differentiation. These features may be of some value in distinguishing ITAC and colonic metastases. Neuroendocrine differentiation in ITAC was associated with higher mortality. Of the five patients with ITAC having 1+ to 2+ chromogranin positivity, only one was free of disease. In contrast, of the seven patients whose tumors lacked more than rare chromogranin positive cells, 6 were disease free.

**Discussion.** Following adenoid cystic carcinoma, the second most common glandular neoplasm of the sinonasal region is composed of cells mimicking normal, adenomatous, or carcinomatous intestinal mucosa (3,5,10-12,16,17,19). Although the histologic spectrum is broad, as discussed above, the clinical features are stereotyped and only slightly affected by the microscopic form of intestinal differentiation. Nasal intestinal-type adenocarcinoma has a strong association with long-term exposure to fine hardwood dusts in the woodworking industry (1,11,14); in such populations the incidence approaches 1000 times that of the general public (1). About 20% of cases occur in patients with industrial wood dust exposure. Exposure to leather dust has also been incriminated (2), as well as several other chemical carcinogens.

There are minor clinical differences between intestinal-type adenocarcinomas occurring sporadically and those arising in woodworkers (3). Tumors related to industrial dust exposure occur predominantly in men (85% to 95%), show a striking predilection for the ethmoid sinus (8,9,14), and have a slightly better prognosis (50% at 5 years) (14). Tumors arising sporadically frequently occur in women, often arise in the maxillary antrum (20% to 50%) and have a worse prognosis (20% to 40% at 5 years) (3). In both groups, the clinical course may be quite protracted and 5-year survival does not indicate cure. Local recurrences are common (53%) (3), and death usually results from uncontrollable local disease with intracranial extension or exsanguination. Metastases to regional lymph nodes occur in about 8% of cases and distant metastases are seen in about 13% (3). Of the microscopic subtypes described below, the papillary form may have a slightly better prognosis or more protracted course than the colon carcinoma-like form, which is in turn slightly less aggressive than the mucinous form (3,5).

Kleinsasser and Schroeder developed a grading & classification system for ITAC which divided the tumors into five groups: papillary tubular cylinder cell (PTCC) grades I & II, alveolar goblet cell, signet-ring cell, and transitional or mixed cell (13). In a study of 79 patients, this grading-classification system appeared to be of prognostic value. Patients with well differentiated PTCC had the highest three-year survival (13). We applied this system to a much smaller group of ITAC (15 cases) and also documented prolonged survival for patients with PTCC-I tumors (7).

As discussed above under immunohistochemistry. Our ongoing studies suggest that the degree of neuroendocrine differentiation in these tumors may also be of considerable prognostic importance (15).

## DIFFERENTIAL DIAGNOSIS

**Metastasis.** When the microscopic appearance of ITAC is that of an exquisitely well differentiated neoplasm, resembling a colonic adenoma or even normal intestinal mucosa, the distinction from a metastasis is not a problem. Corresponding colonic neoplasms are not capable of metastatic behavior. More often, however, ITAC resembles intestinal adenocarcinoma and a metastasis must be considered. Colonic adenocarcinomas have been documented to metastasize to this region. As discussed above under immunohistochemistry, lack of staining for CEA and strong staining for chromogranin are suggestive of ITAC (15). In problematic instances, it is reasonable to perform barium radiographic studies on patients suspected of having primary sinonasal adenocarcinoma resembling colonic

carcinoma.

Low-grade adenocarcinoma. Adenocarcinomas of the sinonasal region that do not resemble salivary-type neoplasms may be subdivided into low-grade adenocarcinomas (10), and intestinal-type adenocarcinomas. The clinicopathologic features of each group differ markedly, warranting distinction. Low-grade adenocarcinomas are a somewhat heterogeneous group, morphologically. In some, the architectural and cytologic uniformity frequently leads to misdiagnosis as an adenoma or papilloma. In the majority of cases, small glands are lined by a single layer of cuboidal or columnar cells, often in a "back to back" arrangement without intervening stroma (10). Some glands are cystically dilated and others contain papillary infoldings. Nuclei tend to be uniform, and mitotic figures are generally rare. Most tumors contain both intracellular and extracellular mucin. Origin from surface mucosa may be seen.

Low-grade adenocarcinoma must be distinguished from intestinal-type adenocarcinoma because of the more aggressive clinical course of the latter lesion. Distinction is usually straightforward, given the nuclear stratification and intestinal appearance of the latter neoplasms. In addition, intestinal-type tumors are cytologically more pleomorphic than low-grade adenocarcinomas with the exception of rare nasal neoplasms resembling normal intestinal mucosa.

Cylindric cell papilloma. Those lesions have an architectural pattern of inverted papilloma but are lined by large cells with eosinophilic, granular cytoplasm. They lack the papillary or complex glandular arrangement and cytologic atypia of adenocarcinoma.

Mucoepidermoid carcinoma. Low-grade mucoepidermoid tumors may have a large mucinous glandular component. The low-power pattern of mucoepidermoid carcinoma, however, consists of sheets of cells with squamous and transitional, as well as mucoid forms.

Acinic cell carcinoma. Acinic cell carcinomas consist of sheets and complex glandular structures composed of rather uniform eosinophilic to clear, cuboidal to columnar cells without cytoplasmic mucus. Cytologically, the cells are quite different from the columnar goblet and absorptive cells of intestinal-like adenocarcinoma.

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## CASE #12

**History.** A 47-year-old woman with a history of sarcoidosis presented with a mass in the left side of the soft palate which had been present for four years. The clinical impression was a benign tumor of minor salivary gland origin. She underwent wide local excision of the mass with placement of a palatal prosthesis.

**Diagnosis.** Plasmacytoid adenoma (plasmacytoid myoepithelioma).

**Follow-up.** The patient is alive and free of disease two years after her excision.

**Microscopic Features.** The tumor is composed of polygonal, "plasmacytoid" cells having large amounts of eosinophilic, hyalinized cytoplasm which, at least focally, displaces the nucleus to the periphery of the cell. Nuclei are round to oval with smooth nuclear membranes and generally inconspicuous nucleoli. Mitotic figures are rare. The plasmacytoid cells form nests and sheets of cells separated by a fibrous stroma. Scattered, more spindled neoplastic cells are present within the cell nests. The stroma is predominantly fibrous with focal myxoid change. In multiple foci, the tumor forms so-called "collagenous spherules." These concentrically laminated or stellate spheres of collagen have been more frequently described in the breast. They have been recognized in salivary tumors, however, and have been said to be associated with myoepithelial cells (21). Obvious ductal epithelial differentiation or chondroid stromal changes are absent from the current case. The margins of the tumor are well-demarcated with at least partial encapsulation. Vascular or perineural invasion is not present.

**Immunohistochemical Findings.** The plasmacytoid tumor cells are immunoreactive for vimentin and cytokeratin. More specifically, the anti-vimentin antibody tends to label the central, hyalinized cytoplasmic mass, and the anti-cytokeratin antibody tends to label the more peripheral portions of the cell cytoplasm. Other cells show more diffuse positivity for both markers. Diffuse cytoplasmic positivity for S100 protein is noted, as well as focal staining for glial fibrillary acidic protein (GFAP) and epithelial membrane antigen (EMA). Stains for desmin, muscle specific actin (MSA) and smooth muscle actin (SMA) are completely negative.

**Ultrastructural Findings.** The cytoplasm of the plasmacytoid cells is filled with aggregates of haphazardly arranged filaments that displace the nucleus and sparse cytoplasmic organelles. Immediately beneath the cell membrane are elongate densities somewhat resembling smooth muscle dense bodies. However, on closer inspection, these are aggregates of intermediate filaments consistent with tonofilaments. Pinocytotic vesicles or true smooth muscle dense bodies are not identified.

### DISCUSSION

The term *myoepithelial* has been very broadly applied to salivary gland neoplasia. In fact, it has even been implied that a neoplastic "myoepithelial" cell need not show evidence of myogenous differentiation (7,8)! In part, this obvious paradox relates to confusion regarding the distinction between the differentiation of a cell, a measurable, objective criterion, and the histogenesis of that cell, at best an unprovable inference. In the past, a main criterion for recognition of neoplastic myoepithelial cells has frequently been S100 protein positivity (4,9,12,15,16,20,23), but this is no longer acceptable (6). A true myoepithelial cell should show combined epithelial and myogenous differentiation.

Salivary myoepitheliomas have traditionally been subclassified into spindle cell and "plasmacytoid" variants, despite a lack of evidence that the plasmacytoid cell type has true myoepithelial features (1-3,5,7,8,13-19,22,24). In fact, the immunohistochemical and ultrastructural features of the plasmacytoid cells in salivary gland adenomas indicate that they clearly lack myoepithelial features. Plasmacytoid cells in these tumors are consistently immunopositive for the epithelial filament cytokeratin, and they do not react with antibodies directed against muscle antigens, including MSA, SMA, and desmin. These antibodies specifically stain normal myoepithelial cells (6,11,25), and the spindle cell myoepitheliomas react with MSA and SMA. The plasmacytoid cells are also immunopositive for vimentin, GFAP, and S100 protein. Immunopositivity for GFAP also does not suggest myoepithelial differentiation. GFAP immunoreactivity has been found in normal salivary intercalated duct and serous acinous cells, as well as myoepithelial cells, and monomorphic adenomas are often GFAP-positive (28). Similarly, although S100 protein reactivity in normal and neoplastic salivary glands has traditionally been

viewed as evidence of myoepithelial differentiation, this has recently been refuted (6). Dardick et al. demonstrated that normal parotid gland myoepithelial cells are MSA-positive but S100 protein-negative.

The electron microscopic findings further support the contention that the plasmacytoid cells lack myoepithelial features (1-3,5;7,8,13, 14,17,19,22,24). To our knowledge, dense bodies characteristic of smooth muscle differentiation have not been described in plasmacytoid cells. An additional finding in our study was the presence of peripheral tonofilaments which corresponded to intense cytokeratin positivity by immunohistochemistry. Barnes et al. also reported tonofilaments in plasmacytoid cells (1).

All studies confirm the epithelial phenotype of the plasmacytoid cells, and we suggest that plasmacytoid "myoepitheliomas" are better classified simply as plasmacytoid adenomas. True salivary gland myoepitheliomas are spindle cell lesions with demonstrable features of myogenous and epithelial differentiation.

**Clinical Features.** There are no clear-cut clinical distinctions between the spindle cell myoepitheliomas and the plasmacytoid lesions. Because these lesions have traditionally been lumped under the same rubric (myoepithelioma), the following is a composite of both tumor types. The age and sex distribution are similar to those of mixed tumor. A review by Barnes, et al. of 41 cases noted the following distribution (1):

MYOEPITHELIOMA
Anatomic Distribution

| Site | # / % of Cases |
|---|---|
| Parotid gland | 21 / 51% |
| Palate | 11 / 27% |
| Submand. gland | 5 / 12% |
| Lip & cheek | 2 / 4% |
| Gingiva | 1 / 2% |
| Retromolar trigone | 1 / 2% |

The tumors present as slowly growing, usually painless masses. Treatment consists of complete surgical resection. As with mixed tumors, lesions of the parotid gland require superficial parotidectomy. Recurrences following complete excision are distinctly uncommon. There have been rare reports of so-called malignant myoepitheliomas (3).

## DIFFERENTIAL DIAGNOSIS

**Mixed Tumor.** The distinction between mixed tumor and "myoepithelioma" of true type or the plasmacytoid variant is somewhat controversial. It is clear that cells similar to both the spindle and plasmacytoid forms may be frequently seen in mixed tumors. Some authors regard the spindle and plasmacytoid lesions as extremes in the spectrum of mixed tumor, an approach with which we basically concur. However, whereas some authors label such tumors as "mixed tumors with prominent myoepithelial cells (sic)," we would prefer to segregate these tumors as spindle cell myoepitheliomas or plasmacytoid adenomas. We reserve the diagnosis of mixed tumor for salivary neoplasms having a clear cut, neoplastic stromal component, often with a prominent myxoid or chondroid quality. From a clinical perspective, this distinction is not, currently, of great importance.

**Multiple Myeloma.** Plasmacytoid adenoma ("myoepithelioma") may be easily confused, at least at first glance, with a plasma cell proliferation. In fact, the author has received cases in consultation with the query of why this "obvious plasmacytoma" did not label with antibodies to immunoglobulin light chains! Antibodies to EMA are well known to label well differentiated plasma cell lesions, so this antibody may add to the confusion in either direction. Strong labelling for cytokeratin will greatly aid in distinction. However, on H&E-stained sections alone, plasmacytoid adenoma lacks the punctate "clock face" nuclear chromatin, amphophilic cytoplasm, and cytoplasmic "hof" (Golgi complex) characteristic of plasma cells.

**Oncocytoma.** The hyalinized cells of plasmacytoid adenoma somewhat resemble oncocytes. However, the former cells lack the prominent cytoplasmic granularity due to mitochondrial hyperplasia (?neoplasia) that characterizes true oncocytes. The cells of oncocytoma also tend to be considerably larger with even more prominent (granular) cytoplasm than the cells of plasmacytoid adenoma. These distinctions can usually be appreciated on H&E-stained sections. If necessary, the strong cytoplasmic positive of the plasmacytoid cells for vimentin and cytokeratin may

be a helpful distinguishing feature. Immunohistochemistry for anti-mitochondrial antibodies will strongly label oncocytes.

**Neurofibroma.** The spindle cell (true) form of myoepithelioma may be confused with a neural lesion (neurofibroma or Schwannoma) arising within salivary gland tissue. This is not as uncommon as might be initially thought; following vascular proliferations, neural lesions are the most common benign mesenchymal tumors of salivary glands. The distinctive patterns of a neurilemoma usually allow for easy recognition, but neurofibromas may cause more diagnostic difficulty. The S100 protein positivity seen in myoepithelioma may add to the potential confusion. Myogenous markers, positive in the spindle cell form of myoepithelioma, will aid in the distinction from a neural lesion. In patients with von Recklinghausen's disease, plexiform neurofibromas of the facial nerve may present as intraparotid masses. The clinically and microscopically distinctive features of these lesions allow for ready recognition.

**Nodular Fasciitis / Inflammatory Pseudotumor / Benign Fibrous Histiocytoma.** There is a group of histologically rather similar fibro-histiocytic proliferations that may rarely arise in the salivary glands. These spindle cell proliferations have been variously labelled as nodular fasciitis, inflammatory pseudotumor and fibrous histiocytoma (26,27). Whether these lesions are distinct entities in the salivary glands or variants of the same process is not clear. The differing names reflect variations in the spindle cell, inflammatory, and histiocytic components. Their microscopic appearance is identical to that of their more common extrasalivary gland counterparts. Confusion with the spindle cell myoepithelium is a recognized problem (26,27). Myoepitheliomas tend to be encapsulated or sharply demarcated lesions, with more "organization and homogeneity" than these lesions (27). Inflammation is not a common component of myoepithelioma. Staining by myoepithelioma for cytokeratin and S100-protein will aid in the distinction, as these markers are negative in this group of lesions (26,27). Strong staining for muscle specific actin is also typical of myoepithelioma, although focal positivity has been demonstrated in so-called nodular fasciitis of the parotid gland (10).

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## CASE #13

**History.** A 6-year-old boy had a one month history of recurrent epistaxis, a 10 lb. weight loss and decreased appetite. Radiographic study showed a large nasopharyngeal mass with extension into the right anterior cranial fossa. An incisional biopsy of the nasopharyngeal mass was performed.

**Diagnosis.** Embryonal rhabdomyosarcoma.

**Follow-up.** The patient was treated with combined radiation therapy and chemotherapy, followed by further excision of his nasopharyngeal and intracranial mass. Seven months later, he was known to have metastases involving both humeri and the lungs. A metastasis in the left humerus was excised. His pulmonary metastases continued to enlarge and he died of respiratory failure 11 months after diagnosis.

**Microscopic Features.** Traditionally, approximately 80% of rhabdomyosarcomas in the head and neck have been embryonal in type, 10% have been alveolar, 5% have had a mixed embryonal and alveolar pattern, and 5% have been so-called sarcoma botryoides. The latter has the microscopic pattern of embryonal rhabdomyosarcoma, and the term botryoides refers only to the polypoid gross appearance of the tumor. The botyroid pattern is commonly encountered when the tumors involve mucosal surfaces such as the nasal cavity and paranasal sinuses, bladder, vagina, etc. The more recently broadened definition of alveolar rhabdomyosarcoma now includes solid variants and tumors with only focal alveolar areas (see below) (37). With these changes approximately 50% of orbital, head and neck and parameningeal rhabdomyosarcomas are of the alveolar type (37).

The histologic spectrum of rhabdomyosarcoma is diverse, and mixtures of embryonal and alveolar patterns in the same tumor contribute to further diversity. Embryonal rhabdomyosarcoma frequently has alternating hypercellular and hypocellular fields. The tumor cells are spindle shaped or spindle shaped to round. Nuclei have a round to oval shape and typically open chromatin with inconspicous nucleoli (37). A pure round cell pattern is not seen in these tumors. Mitotic figures vary considerably in number. Occasionally, there are scattered larger, elongated cells with abundant, deeply eosinophilic cytoplasm and rare, light microscopically detectable cross-striations. Anaplasia, defined as the presence of markedly hyperchromatic nuclei at least three times larger than adjacent cells and clearly abnormal mitoses, may be focally present (16).

Alveolar rhabdomyosarcoma has fibrous septa lined by a single row of neoplastic cells with additional tumor cells lying free between the septa. The neoplastic cells are round with nuclei showing variation in size and shape, usually with coarse chromatin and prominent nucleoli (37). Occasional multinucleated tumor cells with peripheral nuclei may be present. Recently, it has been recognized that some rhabdomyosarcomas lack alveolar structures and consist of closely packed nests of round cells cytologically identical to those lining alveolar septa (36). Sometimes, "nascent" spaces can be noted within the cell nests. No collagenous stroma is present within the nests, but they are separated by dense collagenous bands. This pattern has been called *solid alveolar rhabdomyosarcoma.* The solid areas may be at the periphery of otherwise more typical alveolar rhabdomyosarcomas or they may occur as a pure pattern. The importance of recognizing this variant is that it carries the same higher therapeutic failure rate and correspondingly worse prognosis seen with more conventional alveolar rhabdomyosarcomas, as compared to the embryonal variant (32,37). Even if the alveolar component (either solid or typical) is a minority of the tumor, the prognosis remains relatively poor when compared to embryonal rhabdomyosarcomas lacking any alveolar features (15).

The pleomorphic subtype of rhabdomyosarcoma is characterized by highly pleomorphic cells with more abundant cytoplasm, frequent multinucleation, and often prominent nucleoli (37). A background small cell component is typically present but is often overshadowed by the larger, more pleomorphic cells. Distinction from other "small cell neoplasms" is not problematic. This form of rhabdomyosarcoma is rare, particularly in childhood and, overall, accounts for only a small fraction of all rhabdomyosarcomas. Early descriptions of this variant undoubtedly included other entities such as so-called malignant fibrous histiocytoma (19). Immunohistochemical staining (or electron microscopy) should allow ready recognition of these rare tumors (39).

Recently, an additional, prognostically favorable subtype of rhabdomyosarcoma has been identified and labelled as *spindle cell rhabdomyosarcoma* or as *spindle cell embryonal rhabdomyo-*

*sarcoma* (2,24). The presence of spindled cells is a common feature of most embryonal rhabdomyosaromas and the spindle cell subtype has a specific definition. The latter tumors are characterized by medium-sized, spindled cells, often showing a storiform configuration Cellularity is typically low, and the neoplastic cells have ovoid nuclei with prominent nucleoli. Abundant collagen separates individual tumor cells (24). Some of these tumors may have a distinctly leiomyosarcoma-like or fibrosarcoma-like appearance (24). This subtype accounts for approximately 4% to 7% of all rhabdomyosarcomas (2,24). The paratesticular region is the most common site for this variant, followed by the head and neck region. In the paratesticular region, the 5-year survival for this subtype is 95%, as opposed to 80% for conventional embryonal rhabdomyosarcoma (24). Improved survival is also noted at other anatomic locations. Only "pure forms" of this spindle cell variant have the improved survival. Mixed-pattern lesions have the survival of conventional embryonal rhabdomyosarcoma.

After chemotherapy or radiation therapy, rhabdomyosarcoma can contain a population of "matured" cells with large quantities of eosinophilic cytoplasm. Even this cytologic "differentiation" is a sign of active, persistent tumor, and has been demonstrated in metastases at autopsy (14). Possible hypotheses for this phenomenon have been discussed by Molenaar et al (28).

Cytogenetics. The alveolar subtype of rhabdomyosarcoma has a distinct t(2;13)(q35;q14) chromosomal translocation (10). Other studies have shown loss of chromosome 11 heterozygosity with the embryonal and botryoid subtypes, with retention of the constitutional genotype in alveolar rhabdomyosarcomas (30). These fundamental distinctions reinforce the microscopic separation of alveolar and non-alveolar subtypes.

Immunohistochemical Features. The diagnosis of rhabdomyosarcoma often requires substantiation with immunohistochemical staining (1,6,7,26,29,31,35), or electron microscopy (17). In one study, cross-striations were demonstrable on sections stained with hematoxylin and eosin or phosphotungstic acid hematoxylin in 25%, myoglobin was stained in 50%, and 47% had striations on ultrastructural study (17). One or more of these features were present in 80% of the tumors. The following Table summarizes the literature regarding important immunohistochemical staining in these tumors:

**EMBRYONAL RHABDOMYOSARCOMA**
**Immunohistochemical Staining**

| Reagent | % pos. cases / ref # |
|---|---|
| Myoglobin | 47%-89% (1,6,13) |
| Muscle specific actin | 80% (6) |
| Fast myosin | 67%-87% (6,7,13) |
| Slow myosin | 0%-40% (6,13) |
| Desmin | 100% (13) |
| Creatine kinase/MM | 86% (35) |

Myoglobin is often negative in poorly differentiated, small cell tumors; those neoplasms causing the most diagnostic difficulty (6,7). Accordingly, we find this marker of less value than desmin or muscle specific actin. Recently, antibodies directed against a gene inducing muscle differentiation (MyoD1) have been shown to be shown to be a sensitive marker for rhabdomyosarcoma (8).

Obviously, not all tumors diagnosed as rhabdomyosarcoma are fully documented as having skeletal muscle differentiation (11). Care must be taken to be sure that cells staining for myoglobin are actually cells of rhabdomyosarcoma. Myoglobin from necrotic muscle can be phagocytosed by nonmyogenous tumor cells and histiocytes (12). There have been reports of embryonal rhabdomyosarcomas focally expressing cytokeratin (3,27). The alveolar subtype has been said to be particularly prone to such "aberrant expression," with about two-thirds of cases in one study containing scattered cytokeratin-positive cells, as compared to 23% of embryonal rhabdomyosarcomas (27). Other authors have questioned the reported high positivity for cytokeratin when appropriate antibody dilutions are utilized.

Clinical Features. Rhabdomyosarcoma in the head and neck typically arises in the orbit, nasopharynx, middle ear/mastoid, and nose/paranasal sinuses regions. In some studies, orbital involvement has been most common (34), whereas in other series, tumors arising in the sinuses have predominated (37). Symptoms depend on location and include epistaxis, rhinorrhea, ear pain, or proptosis. Mucosal tumors consist of small red nodules, or a polypoid mass (so-called sarcoma botryoides). About three-quarters of the patients

are 12 years of age or less, but sporadic tumors occur at virtually any age.

The overall five-year survival for all patients with embryonal rhabdomyosarcoma currently is approximately 55% (25). Overall survival for patients with alveolar or mixed rhabdomyosarcoma is approximately 35% at five years (37). It appears to be prognostically important to separate rhabdomyosarcoma into three anatomic groups: the orbit, parameningeal (which includes nose, sinuses and nasopharynx), and other head/neck sites. The five-year survivals for patients presenting with rhabdomyosarcoma confined to these sites at presentation are as follows (25,34): Orbit: 90-92%; Parameningeal: 45-69%; Other ENT: 75-81%.

Cellular "anaplasia" in rhabdomyosarcomas prior to treatment with chemotherapy has also been associated with markedly decreased survival (16). In one study which included alveolar, embryonal and "poorly differentiated" forms of rhabdomyosarcoma (the last group distinct from "pleomorphic" rhabdomyosarcoma), patients with "anaplasia" had a 10% five-year survival, as compared with 65% five-year survival for tumors without anaplasia (16). For their purposes, the authors defined narrowly anaplasia as "nuclear enlargement, hyperchromasia, and mitotic abnormalities" (16). Multinucleated cells were distinct from "anaplasia."

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of embryonal rhabdomyosarcoma includes the family of small cell neoplasms: Ewing's sarcoma, PNET, malignant lymphoma, ofactory neuroblastoma, and others. These can often be distinguished by light microscopy. Nevertheless, immunohistochemistry may be crucial, and sometimes electron microscopy is helpfu, as welll. Malignant lymphoma consists of non-cohesive cells that stain with leukocyte common antigen. Olfactory neuroblastoma usually has neural filaments, and stains for neuronal antigens. Ultrastructurally, neuroblastomas have long, interdigitating cell processes and dense-core secretory vesicles.

**Fetal Rhabdomyoma.** This variant of rhabdomyoma often presents in patients under three years of age, although older patients and adults with this lesion are not rare. The majority are located in the superficial soft tissue in the region of the subcutis. The neck, particularly the posterior auricular region is a common site. Microscopically, the classic form of the tumor consists of lobulated nests of small, embryonic spindled mesenchymal cells, admixed with immature but recognizable skeletal muscle cells, replete with cross striations. The background stroma has a prominent myxoid character. Mitotic activity is sparse and nuclear pleomorphism is minimal. The latter features are critical to distinguishing this lesion from rhabdomyo*sarcoma*. Immunohistochemical stains for myogenous markers, including muscle specific actin, desmin, and myoglobin will be strongly positive, and do not aid in the distinction from rhabdomyosarcoma (18). There have been rare reports of tumors which closely resembled fetal rhabdomyomas on their initial presentation but, in recurrences, were typical embryonal rhabdomyosarcomas (21). Scattered cells of fetal rhabdomyoma may express S-100 protein or GFAP, suggesting a relationship to so-called benign Triton tumor (neuromuscular choristoma) (18). The more mature "intermediate" and adult forms of rhabdomyoma are less likely to be confused with rhabdomyosarcoma (5)..

**Rhabdoid Tumor.** Recently, it has been recognized that embryonal rhabdomyosarcomas may have a focally rhabdoid-like appearance, due to the presence of large cytoplasmic aggregates of intermediate filaments (22). The biologic behavior of these tumors (55% 5-year survival) is indistinguishable from that of conventional rhabdomyosarcoma and considerably better than that of extrarenal rhabdoid tumor (15% 5-year survival), making the distinction of clinical relevance. In rhabdoid tumor, the cytoplasmic inclusions stain for vimentin and cytokeratin, with EMA often positive at the cell membrane (23). Some examples may show occasional cells staining for actin or desmin, but diffuse staining for these markers is absent (23).. In the rhabdoid-like rhabdomyosarcomas, the inclusions stain strongly for actin and vimentin with virtually no cytokeratin staining (22). Staining for muscle specific creatinine kinase and myoglobin, both positive in rhabdomyosarcoma and lacking in rhabdoid tumor, has also been of value (22).

**Ewing's Sarcoma / PNET.** The distinction (if any) between Ewing's sarcoma and PNET is currently problematic, with the former probably representing the least differentiated extreme of the latter. The cells of Ewing's sarcoma are more uniform than those of rhabdomyosarcoma, and have a negligible amount of cytoplasm (9). Ewing's

sarcoma is currently recognized, immunohistochemically, predominantly based on its lack of staining. Any myogenous marker expression excludes this diagnostic possibility.

**Antrochoanal Polyp.** The "botryoid" form of embryonal rhabdomyosarcoma has a distinctly polypoid configuration and, when occuring in the nasal cavity or sinuses, could be underdiagnosed as a nasal polyp. The reverse is far more likely, however. Inflammatory or allergic-type nasal polyps are uncommon in childhood, with the exception of patients having cystic fibrosis. This is the age range most commonly affected by sinonasal rhabdomyosarcoma. In contrast to "allergic" polyps, antrochoanal polyps are common in childhood, increasing the potential for clinical confusion with rhabdomyosarcoma. Furthermore, both "allergic" and antrochoanal polyps, but particularly the latter, may contain scattered atypical to overtly bizarre stromal cells leading to the catastrophic possibility of overdiagnosis as "botryoid" rhabdomyosarcoma (4,33). Microscopically, the changes are similar to those seen in radiation-induced stromal atypia (38). Although the stromal cells are atypical, there is no increase in cellularity or stromal vascularity. A "cambium" layer is not present. The atypical cells have "smudged" hyperchromatic nuclei without mitotic activity. Although seldom necessary, immunohistochemical stains may be of value. The atypical cells of the polyps have been said to have "fibrohistiocytic" features with staining for alpha-1 antitrypsin and lysozyme (20). Staining for myoglobin was negative (20). We are not aware of studies looking for desmin or MSA in these cells, but we would not be surprised if focal "myofibroblastic" differentiation were found. Thus, weak MSA positivity, in particular, should not be overly interpreted in these stromal cells.

**Myxoma.** The myxomatous stroma of rhabdomyosarcoma may lead to an erroneous diagnosis of myxoma. Myxomas virtually never occur in children. A tumor, especially in a child, with a predominantly myxomatous background should stimulate a prolonged search for cells showing muscle differentiation and the use of appropriate immunohistochemical studies.

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## CASE #14

History. A 41-year-old woman presented with nasal obstruction of approximately six months' duration. On physical examination, the upper portion of the nasal cavity was completely filled by a large, deep red, granular tumor which bled easily. The mass extended through the posterior choanae, into the nasopharynx and grew downward, obstructing the right Eustachian tube opening, and displacing the soft palate.

Diagnosis: Malignant melanoma of nasal cavity

Microscopic Features. This case is an excellent example of the "epithelioid" pattern of a mucosal malignant melanoma (see below). As such, its diagnosis may be confused with that of a carcinoma, although in this case the focal pigmentation is a "give away." The tumor is composed of variably sized nests and sheets of large cells with prominent cytoplasm. The latter varies from densely eosinophilic to pale and granular to water clear. The nuclei are large and moderately pleomorphic, with focally prominent, brightly eosinophilic nucleoli. Mitotic figures are easily found. The supporting stroma is highly vascular.

Follow-up. The tumor was initially interpreted as a pigmented, malignant ameloblastoma or a retinal analage tumor. Two months following initial biopsy, a submental lymph node was removed and contained metastatic tumor. Seven months after initial diagnosis, recurrent tumor was removed from both frontal sinuses. Additional tumor was removed from the frontal sinuses approximately 10 months after initial diagnosis. At that time, distant metastases had not been documented.

### DISCUSSION

Clinical Features. Approximately 1% of all malignant melanomas arise in the nasal cavity and paranasal sinuses (1-4,7,8,12,13,16, 18-21,23,25-31). Patients are typically adults, over 50 years of age. There is no male or female predilection. Presenting complaints are non-specific, typical of a nasal mass, and include obstruction, epistaxis, and pain. Favored locations for sinonasal malignant melanoma, in decreasing order of frequency, include the ethmoids, nasal cavity, maxillary antrum, and sphenoid sinuses. Within the nasal cavity, SMM predilects the anterior nasal septum, as well as the middle and lower turbinates.

Complete excision is the treatment of choice, as radiation and chemotherapy have had little or no value. Five-year survival is approximately 10%, and median survival is 2 years. Death is typically due to both widespread metastases and persistent or recurrent local disease with intracranial extension. Five-year survival should no be equated with cure, as a significant number of tumor-related deaths occur after that time (8,13,18,23,27,29).

Pathologic Features. Sinonasal malignant melanoma (SMM) often has a grossly polypoid configuration. On cut section, areas of grossly visible pigment may be present, although many microscopically pigmented examples lack gross pigmentation.

Common microscopic patterns encountered in SMM include (in order of decreasing frequency) small blue cell, spindle cell, epithelioid, and pleomorphic (7). Other patterns may be encountered less commonly, including one in which dissociated cells have prominent, refractile eosinophilic cytoplasm and eccentrically placed nuclei, mimicking rhabdoid tumor or epithelioid sarcoma. Each of these patterns is associated with specific differential diagnoses (see below).

About 30% of SMM are microscopically weakly pigmented or nonpigmented, causing considerable diagnostic difficulty (see below) (7). Junctional change, a helpful diagnostic feature, is present in only about one-third of cases, due to frequent surface ulceration (7). In the absence of intact surface mucosa, junctional change should be sought surrounding the underlying seromucinous glands. A nesting or theque-like growth pattern is also suggestive, but is, again, seen in only about one-third of cases (7).

Immunohistochemical Features. Strong immunohistochemical staining for S-100 protein, vimentin, and with HMB-45 is typical of SMM and is of considerable diagnostic value (5-7,10,11, 14,22,30). Rare SMM may contain scattered cells positive for cytokeratin and epithelial membrane antigen, but diffuse staining, as seen in carcinomas, is absent (7,28,31).

## DIFFERENTIAL DIAGNOSIS

**Olfactory Neuroblastoma.** In our experience, confusion of SMM with olfactory neuroblastoma is most common. One should be particularly suspicious of the latter diagnosis in tumors occurring low in the nasal cavity, beyond the realm of normal olfactory mucosa. A number of factors conspire to further the confusion created by H&E-based similarities. Rarely, SMM may exhibit a distinctly fibrillar background, as well as forming structures resembling Homer Wright rosettes of olfactory neuroblastoma. Focal staining for neurofilament may also be encountered in SMM. Conversely, olfactory neuroblastomas may contain scattered S-100-positive cells, particularly at the periphery of well-formed cell nests (5,15). The diffuse S100 positivity of malignant melanoma is lacking in these tumors, however. Furthermore, olfactory neuroblastomas lack any staining with HMB-45, in our experience (7,30).

**Malignant Lymphoma.** The small cell pattern of SMM, in the absence of pigmentation (a common scenario), is virtually indistinguishable from malignant lymphoma on H&E-stained sections. Because of the markedly different treatment modalities and associated prognostic differences, this distinction is of considerable clinical importance. Application of appropriate immunohistochemical stains for lymphoid neoplasia (LCA, etc) will allow ready distinction. The pitfall is to forget to consider the possibility of malignant melanoma. It is, arguably, malpractice in today's environment to diagnose an extranodal lymphoma without confirmatory immunohistochemical studies.

**Rhabdomyosarcoma.** As with malignant lymphoma, the small cell pattern of SMM may be indistinguishable from embryonal or solid alveolar rhabdomyosarcoma. Both tumors may present as polypoid lesions, although rhabdomyosarcomas are typically (but not invariably) childhood tumors and SMM tend to occur in older adults. Again, considering the possibility and applying appropriate immunohistochemical stains will allow ready recognition. As discussed elsewhere in this course, embryonal/alveolar rhabdomyosarcomas will at least focally express myogenous markers, particularly muscle specific actin and desmin. They obviously lack staining for S100 protein or HMB-45.

**Melanotic Neuroectodermal Tumor of Infancy.** This very rare, benign, partially melanocytic tumor is known by a great variety of synonyms, including retinal analage tumor, melanotic progonoma, melanotic adamantinoma, melanoameloblastoma, and pigmented epulis. Over 95% of cases present in the head and neck region. About 70% arise in the maxilla, 6% in the mandible, and 10% within the skull. Over 95% of patients are in their first year of life at the time of presentation. Up to 45% of these tumors may recur locally, but metastases from head and neck primary tumors virtually do not occur (17). The intraosseous origin and occurrence in the first year of life are clear-cut clinical distinctions from SMM. Microscopically, melanotic neuroectodermal tumors have a stereotypical tubular/alveolar pattern with a biphasic population of small, neuroblastoma-like cells and larger, pigmented cells. Immunohistochemically, the tumors show a highly specific staining pattern with strong positivity for cytokeratin and HMB-45 in the larger cells; synaptophysin, NSE and other neural markers stain primarily the smaller cell population (17,24). S100 protein positivity is rare, and mainly confined to the smaller cells (17,24).

**Lymphoepithelioma / Undifferentiated Carcinoma.** The epithelioid pattern of SMM may be confused with carcinoma, particularly the lymphoepithelioma-like neoplasms. The syncytial growth of SMM, often coupled with a prominent inflammatory stroma can closely mimic lymphoepithelioma. Location of the tumor is of value. SMM, as the term implies, is a sinonasal lesion and lymphoepithelioma almost invariably arises in the nasopharynx, or tonsil. As noted above, SMM may rarely show weak cytokeratin positivity and, conversely (7), lymphoepithelioma may show patchy S-100 protein staining. Diffuse S-100 positivity and HMB-45 staining are diagnostic of SMM. This distinction is of considerable clinical importance, given the relative radiosensitivity of lymphoepithelioma.

**Sinonasal Undifferentiated Carcinoma (SNUC).** This high-grade form of carcinoma is composed of intermediate to larger cells with moderate amounts of eosinophilic cytoplasm and large nuclei with often prominent nucleoli (9). The tumor often grows in a distinctly nesting pattern. The resultant image may strikingly mimic that of a

malignant melanoma. Rare cells in SNUC may be S100 protein positive, but diffuse or strong positivity is absent (9). SNUC express cytokeratin and EMA in most cases, although staining may be somewhat focal. SNUC occurs in a broad age range. Like sinonasal malignant melanoma, SNUC is a rapidly progressive, highly fatal neoplasm that responds poorly to conventional means of therapy. Accordingly, distinction of SNUC from the "better behaved" olfactory neuroblastoma is of more clinical importance than its distinction from malignant melanoma.

**Other Sarcomas.** The spindle cell pattern of SMM may be confused with a sarcoma such as malignant fibrous histiocytoma or fibrosarcoma. Malignant melanomas may also have a distinctly "rhabdoid" appearance mimicking rhabdoid tumor or epithelioid sarcoma. Typically, consideration of the correct diagnosis, coupled with immunohistochemistry allows for straightforward distinction.

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## CASE #15

**History.** A 72-year-old woman presented with a 3-month history of tenesmus with decreasing stool caliber. Colonoscopy demonstrated an intraluminal adenocarcinoma. Abdominal CT-scan showed an "omental cake" and diffuse abdominal metastases. Ascites were also noted. She had had an abdominal hysterectomy and unilateral salpingo-oophorectomy a number of years earlier. At the time of laparotomy, tumor diffusely involved the serosal surfaces of the abdomen, with extension through the colon in the region of the sigmoid. The omentum was densely replaced by tumor. The remaining right tube and ovary had serosal involvement by tumor. A debulking procedure was performed.

**Microscopic Features.** Microscopically, this tumor has the classic features of a serous papillary adenocarcinoma. Its distinction from serous ovarian papillary carcinoma (SOPC) with dissemination is based on the gross and microscopic ovarian findings. The tumor has focally well-formed glands and papillae in a desmoplastic stroma with clear-cut invasion of omental fat. Psammoma bodies are present in variable numbers. The tumor cells are moderately to markedly pleomorphic, and have a cuboidal to low columnar shape with moderate amounts of eosinophilic cytoplasm. Mitotic figures, including atypical forms, are easily found. Necrosis is focally present. The small excrescences on the surface of the ovaries were seen, microscopically, to be small foci of neoplasia confined to the ovarian surface, without invasion of the underlying stroma.

**Diagnosis.** Serous surface papillary carcinoma (SSPC).

**Clinical Features / Biologic Behavior.** It is now well accepted that serous papillary adenocarcinomas microscopically identical to their ovarian counterparts can arise from the peritoneal surface (4,6,9,11-13,15). By definition, these serous surface papillary carcinomas (SSPC) have only minute macroscopic or microscopic ovarian involvement with little or, preferably, no invasion of the underlying stroma (6,9,15). Although it has been argued by some that these small foci of ovarian involvement are, in fact, the primary site of neoplasia, this argument cannot be applied to SSPC with no ovarian component or patients who have had prophylactic oophorectomies because of strong family histories of ovarian carcinoma and later developed SSPC (12). Furthermore, areas of SSPC often show apparent transitions from normal mesothelium to atypical serous mesothelium and overt carcinoma (6), and microscopically identical serous neoplasms have been described arising from the tunica vaginalis in males (2,14).

SSPC seem to be associated with other forms of Mullerian neoplasia. Gooneratne et al. documented endometrial neoplasia in 3 of 16 SSPC and a fourth patient had an occult endometrioid ovarian carcinoma (6). Three of 10 patients in our study, had endometrial serous papillary adenocarcinoma and a fourth had intramucosal serous carcinoma of the fallopian tube (9). We interpret these multiple lesions, at least in most instances, as separate primary neoplasms, suggesting that SSPC is associated with a "field effect" for Mullerian neoplasia.

Given its apparent origin from the peritoneum, some authors have suggested that SSPC be considered as a mesothelioma (10). Indeed, similar arguments have been presented for ovarian serous neoplasms (10). Regardless of their origin, it seems clear, based on light microscopic, ultrastructural, and immunohistochemical features (discussed below) that SSPC is an "epithelial" neoplasm with features which allow distinction from mesothelioma. Lumping SSPC with mesothelioma would also obscure epidemiologic studies dealing with asbestos and other carcinogens.

SSPC are invariably Stage III or IV neoplasms. The mode of presentation is identical to that of high stage SOPC or peritoneal malignant mesothelioma. Abdominal distention, pain, and ascites are invariably present. Initial studies of SSPC suggested that these tumors had a significantly poorer prognosis than SOPC (6,15). A study of 10 SSPC from our institution, compared to 16 stage-matched SOPC, treated by identical protocols, seemed to confirm that finding (9). The median survival for SSPC in our study was 12 months, as compared to 24 months for SOPC. All 10 patients with SSPC in our study were dead at 52 months, whereas the predicted five-year survival for patients with SOPC was 23% (9). Other studies have shown no apparent difference in prognosis for SSPC and stage-matched SOPC (4). Most recently, a relatively large series (n=29) of SSPC again showed a poorer prognosis when compared to stage-matched SOPC. The median survival time was 19 months for SSPC vs. 31 months for SOPC;

disease-free intervals were also significantly shorter for SOPC (8).

Differential Diagnosis. The light microscopic features of this case, particularly the focally columnar nature of the tumor cells, allows for distinction from malignant mesothelioma. Raju et al, in a comparative study of SSPC and malignant mesothelioma noted that SSPC typically had well differentiated papillae with distinct fibrovascular cores, columnar, crowded cells with overlapping nuclei having their long-axis perpendicular to the papilla, and numerous psammoma bodies (11). In contrast, epithelial malignant mesotheliomas have tubulo-alveolar structures, solid cell nests, poorly formed papillae lined by well-spaced cuboidal cells without nuclear overlap, no nuclear polarity, and infrequent psammoma bodies (11).

In some instances, however, the tumor cells in SSPC may be reminiscent of mesothelium, and the florid desmoplastic stroma may suggest a biphasic neoplastic component. In such cases, immunohistochemistry (or electron microscopy) may be of value in making the distinction of serous carcinoma and malignant mesothelioma. Electron microscopy, considered in the past as the "gold standard" is more time consuming, expensive, and suffers from sampling error. Ultrastructurally, the cells of mesothelioma have elongated, often branched surface microvilli with a length to diameter ratio (LDR) of 10 to 1 or greater. Cells are closely apposed and bound by well-formed junctional complexes. Broad aggregates of intermediate filaments are usually present (3). Serous carcinomas have microvilli with lower LDR's and do not contain well-formed bundles of tonofilaments.

Histochemical and immunohistochemical stains can be of considerable value in distinguishing serous carcinoma and malignant mesothelioma. As can be seen from the table below, neutral mucin positivity is of some value in this regard, but there is an associated high false negativity. CA-125, although a good marker of Mullerian neoplasia, is also positive in malignant mesothelioma. This should not be surprising, given the known elevation in CA-125 in association with peritonitis. The best immunohistochemical markers currently available for distinguishing peritoneal malignant mesothelioma and serous adenocarcinoma are B72.3, Leu M1, placental alkaline phosphatase, and CEA. Because the immunohistochemical diagnosis of malignant mesothelioma is essentially one of exclusion, stains for cytokeratin and/or EMA should be performed in tandem with discriminatory stains to verify the antigenic "viability" of the tissue.

**IMMUNOHISTOCHEMICAL STAINING PROFILES**

| Determinant | SSPC (%+) | SOPC (%+) | Peritoneal Epith. Mesothelioma (%+) |
|---|---|---|---|
| Cytokeratin | 100% | 100% | 100% |
| EMA | 100% | 100% | 86% |
| **B72.3 antigen** | **100%** | **77%** | **0%** |
| CA-125 antigen | 85% | 90% | 14% |
| S100 protein | 100% | 94% | 11% |
| **Leu M1** | **77%** | **71%** | **0% (*)** |
| **Placent.alk.phos.** | **38%** | **61%** | **0%** |
| Amylase | 15% | 32% | 18% |
| **CEA** | **8%** | **16%** | **0%** |
| **Neutral mucin** | **50%** | **50%** | **0%** |

Based on studies of 13 SSPC, 31 SOPC, and 28 mesotheliomas in two reports (3,16). (*) 3 of 28 malignant mesotheliomas expressed very focal staining with Leu M1, no mesothelioma showed diffuse staining (3).

Other "markers" including human milk-fat globulin (HMFG-2), blood group antigens, vimentin, epithelial membrane antigen, and various lectins have also been applied to the distinction of mesothelioma and adenocarcinoma. In our experience, these have not been as helpful as those markers highlighted above, particularly CEA, Leu M1, and B72.3. HMFG-2, originally touted as

valuable adenocarcinoma discriminant, has more recently been reported as positive in a high percentage of mesotheliomas (7). It seems likely that the list of useful discriminating antibodies/antigens will continue to grow, however. Recent adenocarcinoma determinants awaiting further study in this regard include Ber-EP4 and BRST-1. Currently, the immunohistochemical diagnosis of malignant mesothelioma remains one of exclusion. What is most needed is a mesothelioma-positive marker which works on paraffin-embedded tissue and does not cross-react with any adenocarcinomas.

It should be noted that, at this time, immunohistochemistry is of no value in distinguishing mesothelial hyperplasia from malignant mesothelioma. Likewise, immunohistochemistry is currently of no value for distinguishing endosalpingiosis, borderline serous proliferations, and serous carcinomas. Flow cytometry holds some limited promise for the distinction of reactive and proliferative mesothelial lesions. In our experience, reactive mesothelial proliferations invariably have been diploid, but only 53% of malignant mesotheliomas were aneuploid (5). Thus, although aneuploidy strongly suggests malignancy, diploidy does not exclude it.

Distinguishing SSPC from benign serous "metaplasia" of the peritoneum, also known as endosalpingiosis, should not be a diagnostic problem. Endosalpingiosis consists of benign glands resembling normal tubal epithelium. Although there may be rare papillations and nuclear pseudostratification, pleomorphism is minimal and mitotic figures are rare. Occasionally, more exuberant serous proliferations with features analogous to ovarian borderline tumors may involve the peritoneum, often in association with endosalpingiosis, but with little or no ovarian disease (1). The desmoplastic variant of these serous borderline peritoneal tumors may be easily confused with SSPC. However, the desmoplastic borderline lesions are "stuck on" the peritoneal surfaces with smoothly contoured margins and no evidence of destructive invasion. Although such desmoplastic foci may extend between the septa of omental fat, they maintain their smooth marginal contours (1). Borderline serous peritoneal tumors may manifest moderate nuclear pleomorphism, but mitotic figures are absent or very infrequent. Distinction of peritoneal serous borderline tumors from SSPC is important. Of 25 patients studied by Bell & Scully, only four developed recurrent disease (1). Two recurrences remained borderline lesions and two progressed to serous carcinoma. This biologic behavior is clearly quite different from that of SSPC.

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# CASE #16

**Lobular Carcinoma In Situ**

The term carcinoma in situ was coined by Broders in 1932, and he illustrated an indubitable case of lobular carcinoma in situ.[4] The term "lobular carcinoma in situ" was first used by Foote and Stewart in 1941,[18] but it was not until the late 1960's and early 1970's that lobular carcinoma in situ (LCIS) was widely recognized in the pathology community. Debate continues as to the (1) definition of what is included in LCIS and (2) whether the term "lobular neoplasia" is better than LCIS. We are in the habit of using the term LCIS, because our surgeons do not consider it to be a true carcinoma any more than we do. The term lobular neoplasia, however, has considerable merit and is encouraged for surgeons who take the diagnosis of LCIS to literally mean "genuine carcinoma."

LCIS should be viewed as a morphologic expression of a state of increased risk for invasive cancer when that patient is compared to the population at large. This risk is approximately 10 times the risk of the general population. LCIS is not to be considered an obligate precursor for invasive cancer.

**Cytology (Quality) and Architecture (Quantity) of LCIS.** The ductules are capable of considerable enlargement due to ordinary hyperplasia. The cells and their arrangement are no different than what is seen in larger ducts with ordinary hyperplasia. Cell boundaries are indistinct, nuclei are predominantly ovoid, and irregularly distributed. They frequently overlap. By contrast, LCIS is populated by a clearly monomorphic population of cells. They have round nuclei, powdery cytoplasm, well defined cell borders, and are evenly spaced one to another. The overlapping, irregular appearance of hyperplasia is missing. In addition to this population of small, uniform cells, larger abnormal cells have been included in the definition.[33] There may be a mixture of large and small cells in the same ductule. A modest amount of pleomorphism is thereby permissible. Typically, the cells are closely approximated, but sometimes they lack cohesion. The ductules should be enlarged and the lumen obliterated. When a monomorphic population of cells with distention and lumen obliteration occupies more than half of the ductules of a single lobule, the diagnosis of LCIS can be made. Although the ductules of only half the lobule have to be distended, the entire lobule must be populated by the characteristic cells.[29]

Target cells have a clear, round space in the cytoplasm. If there are sufficient secretions in the space, an eosinophilic dot is seen. Ultrastructurally, the lumens are lined by a cell membrane and do not communicate with extracellular stroma or other cells. Target cells are seen rarely in ordinary hyperplasia, and, in effect, they are almost pathognomonic of LCIS.

**Prevalence of LCIS.** The prevalence of LCIS is not known. In 200 patients undergoing breast reduction, seven cases of LCIS were found by submitting two to 40 blocks.[3] Six of 70 patients (8%) beyond the age of 40 had LCIS. In a medicolegal series, five out of 110 (4%) of women had LCIS.[25] In another series, none of 101 women had LCIS although 9% had DCIS.[1] The subgross method of examination was used.

**Risk for Subsequent Invasive Carcinoma.** Risk for subsequent invasive cancer in a patient with otherwise untreated LCIS has ranged as high as 30%.[33] The invasive carcinomas have been in the contralateral breast in 50% of patients. Nevertheless, some series have not found a strikingly high risk. In one series, only one of 25 women followed for an average of 17 years developed invasive carcinoma.[36] In this same series, there were 31 women who had been treated with mastectomy for LCIS. Three of these 31 women (9.7%) with a contralateral breast at risk developed invasive carcinoma from 10 to 13 years after LCIS in the opposite breast. This figure is similar to the 8.5% found by Haagensen.[20] Eusebi et al. recently reported 13 women with a minimum of 14 years follow-up, none of whom has developed invasive carcinoma after the diagnosis of LCIS.[13] They admit that the small sample makes this experience of limited value. Conversely, a recent study of 69 incidentally found LCIS showed that 8 (12%) patients developed invasive cancer within 42 months.[27]

Page et al. found a risk of 17% invasion at 15 years.[30] In most series, the invasive

carcinoma has been infiltrating ductal type. In the series by Page et al., seven tumors were infiltrating lobular (three classical, four variants); two were tubular, and only one was infiltrating ductal. This may reflect the fact that Page requires, for the diagnosis of LCIS, the "gold standard" small cell uniform population with major distention of ductules. Less classical images constitute a fair number of cases in other series, and although they correlate with an increased risk for cancer, they do not necessarily select for a high risk of infiltrating lobular carcinoma.

A family history of invasive carcinoma and the use of estrogens does not correlate with an increased risk.[30,33]

**Lobular Carcinoma In Situ in Fibroadenoma.** By 1985, about 100 cases of either noninvasive or invasive carcinoma had been reported in fibroadenomas.[28] Approximately half of the carcinomas have been LCIS, 35% have been infiltrating (either infiltrating lobular or infiltrating ductal), and 15% have been ductal carcinoma in situ (DCIS). The DCIS is usually a small cell cribriform or micropapillary carcinoma. Comedocarcinoma is rarely found.

In one series, carcinoma was found in two of 73 fibroadenomas removed from women between the ages of 40 to 60.[6] About 40% of patients with LCIS in a fibroadenoma have LCIS in the breast tissue adjacent to the nodule. Carcinomas arising in fibroadenomas do not seem to differ from the corresponding form of carcinoma arising *de novo*. For example, some patients with LCIS in a fibroadenoma have had long term disease-free intervals without further therapy. Others have subsequently developed invasive carcinomas either in the ipsilateral or contralateral breast. Based on this information, it seems reasonable to treat a patient with LCIS in a fibroadenoma the same way that one would treat a patient who had the diagnosis of LCIS in the absence of a fibroadenoma.

**Lobular Carcinoma In Situ in Sclerosing Adenosis.** LCIS in sclerosing adenosis can raise the issue of invasive carcinoma.[15] It may mimic the alveolar variant of ILC. The diagnosis of sclerosing adenosis as the background lesion is critical. The ductules at the periphery of sclerosing adenosis tend to be larger than those centrally. There is a rounded or pushing low power margin. Sclerosing adenosis is accompanied by fibrous tissue to the edge of the focus. The epithelium of sclerosing adenosis virtually never extends into fat unaccompanied by fibrous tissue. On the other hand, infiltrating carcinomas usually have at least a few epithelial cells insinuated in the fat beyond the desmoplastic response.

A much more difficult problem is when there are small ductules in sclerosing adenosis that are not distended. The cells may appear to be in single file or form such small tubules that they look like aggregates of invasive carcinoma. The lack of a desmoplastic response, and the recognition of a faint architecture of sclerosing adenosis are the only features that are helpful.

**Treatment of Lobular Carcinoma In Situ.** The therapy of LCIS depends on how one views its natural history. As time has gone by, it is obvious that the majority of patients with LCIS never develop invasive cancer. Moreover, at least 60 to 70% of invasive cancers that develop are not lobular carcinoma. As Gump has pointed out, "The small round cells [of LCIS] with pale cytoplasm that fill and distend the acini are not the enemy."[19] They are a marker of increased risk for invasive cancer when compared to the risk in the population at large. If LCIS is found in a biopsy, there is no reason to do a wider excision, because the risk of cancer is approximately equal in both breasts. One cannot surgically excise a "risk factor."

Radiation has no role, because one cannot successfully irradiate an increased risk. Tamoxifen has been suggested as therapy. There are no data as to its long-term benefit (if any), and it appears to cause endometrial carcinoma.

Essentially the options consist of (1) observation (2) subcutaneous mastectomy (3) total mastectomy with or without contralateral biopsy (4) bilateral mastectomy.

A survey of surgeons in 1988 showed that the most common recommendation was observation (55%), the next was unilateral mastectomy (33%), whereas 9% advised bilateral mastectomy. These recommendations are mirrored in reality. About 55% of the

patients accepted observation and 40% had mastectomy. Haagensen was the early champion of observation, noting that the relative risk of observed-to-expected ratio for invasive cancer was 6.9:1. A similar risk ratio exists for women whose mothers have bilateral breast cancer before menopause. Obviously this is of great concern to the daughters, but prophylactic mastectomy is rarely recommended in this clinical setting.

It is probably useful to report the presence of LCIS in a breast that contains any form of invasive cancer. There is a hint that such patients are at greater risk for contralateral cancer than if LCIS were absent.

**Mammographic Findings of Lobular Carcinoma.** LCIS has no distinctive mammographic appearance.[31] When LCIS is found in a mammographically generated biopsy, it is always due to microcalcifications. Infiltrating lobular carcinoma (ILC) often has an unusual x-ray compared to the sharply defined stellate mass that characterizes most infiltrating ductal carcinomas.[17,15] These ILC are "fieldfire" tumors that pepper the breast with tumor cells but fail to make a discrete mass. Mastectomy specimens from such a patient look like normal breast, or there may be scattered fibrocystic changes as a coincidental finding.[22] Diffuse invasive cancers, (most of which are ILC) made up 8% of tumors in one study. In another study, only indirect signs (not a mass) led to biopsy.[23] Almost 25% of ILC lacked a mass in a study of 402 cases. Lack of mass correlated with 100% residual disease after biopsy.[37]

**Infiltrating Lobular Carcinoma.** Invasive lobular carcinoma (ILC) varies from less than 1% to 20% of invasive cancers in different series, which obviously reflects different histologic criteria. Azzopardi stated in his book in 1979, "There was no single criterion which was uniformly valid in the differential diagnosis between ILC and IDC. Several criteria have to be considered together and the overall structure and cytology accorded more importance than any particular fields of tissue."[2] We agree with Page and Anderson that ILC must be recognized as having two basic features, namely the cytology or the pattern of infiltration.[29] These may occur together producing a pure classical ILC, or the cytology and the pattern may be used as individual criteria. In other words, one can use cytologic criteria to the exclusion of architecture, and for other tumors use architectural criteria and disregard cytology.

The amount of a tumor required for the diagnosis of classical ILC (small cell plus single-file or targetoid architecture) has varied in different series. Dixon et al. used 80% or more of the tumor as the threshold, and this seems reasonable.[8,9] Tumors with less than 80% of classical ILC are placed in their "mixed group"; a less favorable prognostic category. Rosen requires 85%.[7]

**Cytologic Criteria.** The strictest cytologic criteria limit the tumor cells to a single population of small cells defined as 8-12 microns.[36] The cells may occur singly or in groups of two or three. The classic single-file pattern often results in distortion of the cell nuclei in which they are molded. The cytoplasm may or may not be demarcated by conspicuous cell membranes as is often seen in LCIS. Target cells occur in about 65% of cases.[6] Target cells are most often seen in ILC, but are not limited to ILC. On occasion, they occur in IDC including cytologically high grade IDC with great pleomorphism. Mitoses are almost never seen in classical ILC. One unpublished study showed that only about 0.5% of cells were in S or G2-M phase. (By contrast, 30-60% of cells in comedocarcinoma are in these phases).

Using only the above cytologic criteria (i.e. small, uniform cells), different architectures of ILC have been described beginning in 1975. These include a solid variant,[10] a tubulolobular variant,[17] and an alveolar pattern.[34] In the original descriptions, all of these subtypes had a population of small, uniform cells. Tavassoli, Page and Anderson, and Rosen do not consider tubulolobular to be a variant of lobular carcinoma.

The pleomorphic variant is diagnosed architecturally. There may be a classic single-file arrangement of cytologically grade 2 or even grade 3 cells. The other architecture that is accepted for ILC is individual scattered cells. These may surround ducts (just as classical ILC may have this "targetoid" architecture). The

cytologic appearance is completely different from prototypical LCIS cells because their size is greater, and as the name implies, there is variation in the size of the nuclei. In addition, there is often considerably more cytoplasm than in the classic, small cell type described above. In contrast to the classical ILC, pleomorphic ILC always has one to three mitoses per 10 HPF.[14]

The problem of classification of pleomorphic ILC is seen in the Legend for Figure 13.46 in the excellent book by Page and Anderson.[29] It reads, "Irregular small aggregates of diffusely infiltrating cancer cells suggest a pleomorphic lobular carcinoma. However, this could also be interpreted as poorly differentiated carcinoma of no special type. Fortunately there is no proven prognostic difference between these diagnoses."

In 1984, Eusebi et al. accepted apocrine differentiation as a part of LCIS.[12] Eusebi et al. recognized an infiltrating variant of pleomorphic lobular carcinoma that has apocrine differentiation and is aggressive. The tumors in their 10 cases ranged from 4 to 8 cm in size and all except one had lymph node metastases. Most patients were dead of disease within three years. The one survivor at two years was the patient with negative nodes, although she had an 8-cm tumor.[14]

**Architectural Criteria.** If one uses only architectural criteria (single file or dissociated, scattered individual cells), there will be a larger percentage of tumors classified as ILC because it will include cytologic score 2 and even score 3 cells such as found by the Nottingham Group.[11] They point out that they have a broad definition of lobular carcinoma, thus resulting in 14% of their invasive cancers being ILC. One of their categories of ILC "has the infiltrative pattern of classical lobular carcinoma but shows cellular atypia and pleomorphism. The cells in this type may also be larger and contain more cytoplasm than in the classical type."

The data from the Nottingham group are very useful because they have studied thousands of infiltrating carcinomas since 1970. They have the advantage of a longstanding standard form of therapy (total mastectomy plus node sampling) without adjuvant therapy of any kind. Parenthetically, this has resulted in a powerfully discriminating prognostic index (calculated as 0.2 x size of tumor + 1-3 node status + histologic grade 1-3).

Infiltrating lobular carcinoma makes up 14% of the operable tumors in Nottingham. Their grades for ILC are: 13% are grade 1, 75% are grade 2, and 12% are grade 3.[10] (They use a modified Scarff-Bloom-Richardson Histologic Grading System as detailed in Page and Anderson pp 300-311).[29]

**Prognosis of Infiltrating Lobular Carcinoma.** The prognosis of classical ILC is better than IDC in the sense there is a longer disease free interval.[8] In the study from Memorial Hospital, patients with stage I ILC had a significantly longer disease-free interval than comparable patients with IDC, but there was no significant difference in disease-free interval with stage II ILC versus IDC.[7] In the Nottingham study, patients with ILC did better than IDC, despite a large number of ILC lesions with Scarff-Bloom-Richardson grade II and even grade III.[11] The patients were not stratified by clinical stage, however. About 80% of ILC are diploid, and 70-90% are ER positive, especially the alveolar variant that approaches 100% ER positivity.[34]

Dixon et al. suggest that there is an increased risk for bilateral invasive cancer in ILC.[9] This is probably the greatest for pleomorphic ILC. They did observe, however, that even with an increased risk of bilaterality, the prognosis does not seem altered when the second tumor is metachronous. Dixon et al found increased risk of bilaterality (20%) for ILC compared to 8% for IDC.[9] In another study carried out between 1970 and 1980, contralateral biopsy was performed in 47 patients undergoing mastectomy for ILC. Random biopsies occurred in 108 patients and directed biopsies in 22 patients. Ten percent of random contralateral biopsies revealed invasive cancer, and another 6% had DCIS. Corresponding figures for the directed biopsies were 32% and 5% respectively.[35] The finding of multicentric invasive disease in the ipsilateral breast was a significant predictor of positive contralateral biopsy. The age and nodal status of the ipsilateral mastectomy had no effect on the findings of contralateral disease. The authors suggest routine, random contralateral biopsy in

patients with ILC.

The distribution of metastases of ILC differs from IDC.[21] This suggests a difference in the biologic behavior, which warrants narrative separation of ILC and IDC (rather than merely relying on grade). For example, metastases to the adrenal were seen in 91% of patients with ILC as opposed to 58% of patients with IDC.[5] Multiple endocrine organ involvement was more common in ILC than IDC.[5] Bone metastases are much more common in ILC and were the most frequent site in the series from Memorial Hospital.[7] IDC tends to metastasize to the parenchyma of the CNS, whereas ILC has a predominantly meningeal spread. Another striking tendency is to metastasize to the peritoneal surface. ILC (including SRC) evokes a pronounced desmoplastic reaction with invasion into the underlying gut wall.

**Prognosis of Variants of Infiltrating Lobular Carcinoma.** The variants include solid, alveolar, and mixed, and proportions vary from series to series.

Dixon et al. found that the classical ILC did well compared to the variants as a group. This held up even when the clinical stage of disease was removed as a variable.

The Memorial group also concluded that there was a trend for the variant tumors to behave worse than classical ILC.[7] Their results, however, were not statistically significant. Conversely, the Nottingham group found that tubulolobular and alveolar did significantly better with 80% to 90% survival at 10 years.[11] (This contrasts with 60% for classic and mixed types.) The numbers in each subtype are small (except for the mixed group) and additional cases are needed. The mixed group paralleled the survival curve for classical ILC. In a study from Norway, 13 of 163 had an alveolar component.[25] This ranged from less than 25% to more than 75% of the tumor. There was no discernible difference regarding nodal status, distant metastases, or overall survival when compared to the classical ILC.

Data from three major studies that have looked at prognostic significance are summarized as follows:

**RATIO OF CLASSICAL TO VARIANT ILC**

| | Dixon et al.[6] | Memorial[7] | Nottingham[11] |
|---|---|---|---|
| CLASSICAL | 31 (30%) | 176 (77%) | 97 (40%) |
| VARIANT | 72 (70%) | 54 (23%) | 146 (60%) |

**Signet Ring Carcinoma.** Signet ring carcinoma (SRC) is viewed by most as a variant of ILC.[24] Merino and LiVolsi felt that SRC was properly considered a variant of ILC because of its single-file pattern and high association (46%) with LCIS. They classified a tumor as SRC when 20% of the tumor had signet cells. One case had signet cell CIS. A signet ring cell is not the same as a target cell. A signet ring cell has the cytoplasm almost completely replaced with mucin pushing the nucleus to the periphery of the cell. A target cell may have the nucleus at the periphery of the cell, but this is because it contains an intracytoplasmic lumen. The two types of mucus-secreting cells can occur in the same tumor.

Fourteen of 24 patients with signet ring cell carcinoma were dead of disease; seven surviving less than one year. The eight alive without disease at the time of reporting had been followed from one to four years.[24]

Raju et al noted that the metastases in two patients contained signet ring or target cells whereas the primary consisted of prototypical small cells lacking these features.[32] In all of their ten breast cancers with signet ring features

the GCDFP-15 was positive. Only five of ten prototypical ILC lacking signet cells were positive for GCDFP-15. GCDFP-15 is a fairly specific marker for breast cancer, at least when it presents in sites that might otherwise be considered primary. None of ten signet ring carcinomas of the stomach and none of two signet ring carcinomas of the colon stain with GCDFP-15. Five of the ten cases with signet ring features had unusual metastatic patterns, namely the pattern seen in ILC in general. They concluded that the presence of GCDFP-15 in some ILC without signet ring cells plus the distribution of metastases indicated that signet ring carcinoma was "usually a variant of lobular carcinoma and not a distinct entity."

Signet ring cells sometimes predominate in metastases, even in the absence of signet ring cells in the primary tumor. This attests to the morpho-functional heterogeneity of lobular carcinoma.

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## CASE #17

### Apocrine Ductal Carcinoma In Situ

The abundant granular cytoplasm of apocrine epithelium is due mainly to osmiophilic droplets that are membrane-bound. The apocrine snouts can contain droplets or merely the cytoplasmic protrusions devoid of droplets. The cells also have many mitochondria, but these are not nearly as numerous as in oncocytes.[9,12]

The case that you have available for study has involvement of the lobules as well as the large ducts. Apocrine metaplasia begins in the ductules of individual lobules and on occasion is seen in lobules that are of normal size. Apocrine-lined ductules are a proliferative process, and they enlarge to form the widely dilated ducts and the grossly apparent cysts that we see so frequently.

In the case under discussion, there is involvement by neoplastic epithelium at every level of the lobular and ductal system. Ductules without distention show markedly abnormal cells with high nuclear cytoplasmic ratios and nuclear abnormalities. The latter are most conspicuous as irregularly shaped vesicular nuclei. In the larger ducts, there are other patterns of ductal carcinoma in situ (DCIS). These include bands of epithelium that bridge the ducts. Bridging bands are rarely seen in ordinary hyperplasia, and any bridge of epithelium across a duct lumen should raise the possibility of DCIS. This must, of course, be accompanied by the proper cytologic population of cells.

Rare foci of necrosis are seen in your case. These are tiny aggregates of cytoplasm and nuclear debris. They must be searched out at medium or high power. When present, they are an invaluable aid to making the diagnosis of apocrine DCIS. For practical purposes, they can be considered pathognomonic of DCIS.

Noninvasive apocrine carcinoma poses a special problem because of the cytologic spectrum of pleomorphism that ordinary, benign apocrine metaplasia assumes. Cytologically, apocrine metaplasia may have nucleoli that are often large, and the nucleoplasm is frequently clumped along the nuclear membrane. Architecturally, apocrine metaplasia has little variation. Even the largest cysts are often lined only by a single layer of columnar apocrine cells. The only complex formations are small tufts three to five cells thick and occasional tufts with a single capillary, thus forming a true miniature papilloma. More complicated configurations do not occur such as interconnecting bridges, columns of cells crossing the duct lumen, or markedly elongated papillations in contrast to the small tufts just mentioned. It is this limited array of architectural expressions that is the major clue for recognizing different proliferations that are of important biologic potential compared to ordinary apocrine metaplasia.

Apocrine ductal carcinoma in situ (DCIS) can assume most of the patterns found in DCIS lacking apocrine features including solid growth, irregular cribriform pattern, papillary (with distinct fibrovascular cores), micropapillary, and a solid pattern. The only pattern that apocrine DCIS lacks is the sieve-like pattern of cribriform DCIS composed of small cells that form small, round lumens. Many comedocarcinomas are characterized by cells having eosinophilic cytoplasm and could be considered apocrine cells, but these are excluded from this discussion because they pose no diagnostic problem.

There are two main cytologic trends in apocrine DCIS. Paradoxically, I have observed that architecturally typical apocrine DCIS is often composed of cells that are actually more uniform than the spectrum seen in apocrine metaplasia. Page et al. noted that the cells of apocrine DCIS lacked a vesicular appearance.[11] To be sure, some cases have considerable pleomorphism.[1] The other cytologic appearance is the presence of cells with apparent increased nuclear/cytoplasmic ratio in which the nucleus is located in the apical portion of the cell and "attached" to the basement membrane by a narrow width of cytoplasm. This creates a hobnail appearance and can involve the ductules within a lobule as well as the large ducts. These cells frequently have dense nuclei in which the nucleolus is obscured or completely unrecognizable. There is considerable pleomorphism when this cytologic population is present. Often the nuclear/cytoplasmic ratio is high.

Architectural types of apocrine DCIS vary. The irregular cribriform pattern with its complex interconnecting bridges and vertical papillations is easily recognized. A much more subtle but

equally diagnostic pattern is to have ducts (often small ones) completely filled with apocrine epithelium. This is a phenomenon that does not occur in ordinary apocrine metaplasia. A lesser form of duct involvement by apocrine DCIS is to have a concentric mural layer of cells three to five cells thick without any tufting. Finally, apocrine DCIS may occur simultaneously in a duct with a papilloma. The papilloma is lined by conventional low or tall columnar epithelium that has scant cytoplasm. The apocrine cells stand out because of their voluminous cytoplasm, more complex architecture (the irregular cribriform architecture), and often thin strands of attenuated cells making looping bridges. The latter may be seen in the irregular cribriform apocrine DCIS that involves ducts. This is somewhat paradoxical in that it is not the "stone-like" rigid bridge architecture of small cell DCIS. It fits the description of "streaming," a criterion that is often used to characterize the epithelial proliferation of ordinary hyperplasia. It should be emphasized, however, that the streaming that takes place in ordinary hyperplasia does not form these "bucket handle" or "looping bridges" that occur in apocrine DCIS.

The biologic behavior of apocrine DCIS is analogous to other noncomedo types of DCIS. Abati et al. found recurrence in three of 20 patient treated by biopsy alone.[1] However, one feature is shared with comedo-type carcinoma, to wit, one patient had axillary metastases at the time of treatment by mastectomy and died of disease five years later. This frequency of one in 55 is similar to the approximate 1% rate in which axillary nodal metastases are found in patients with comedocarcinoma without identifiable invasion. In the recently published series by Tavassoli and Norris, two women treated with lumpectomy for apocrine DCIS developed invasive carcinoma 2.5 and 4 years later, respectively. The original lesions are not illustrated, but were said to show necrosis.[16]

I have seen several cases of infiltrating apocrine carcinoma that contained apocrine DCIS with one or more patterns of the above. Often, infiltrating apocrine carcinoma lacks apocrine DCIS but may be accompanied by lobular CIS[1] and apocrine sclerosing adenosis.

Apocrine metaplasia in sclerosing adenosis can raise the question of invasive apocrine carcinoma.[2,3] One must fall back on the architecture of the lesion recognizing that sclerosing adenosis has very little architecture. Nonetheless, in sclerosing adenosis, there is a tendency for the cells to be arranged, at least focally, in fairly evenly spaced parallel rows, and the ductules at the periphery of the sclerotic foci tend to be mildly dilated. Thus, when atypical cells (including apocrine epithelium) are seen within such foci, they can be distinguished from an invasive lesion. Often, it is possible to find individual ductules partly lined by the large, pleomorphic apocrine cells and partly lined by ordinary epithelium. If one is lucky enough (and this doesn't happen as often as one would like), there may be a recognizable myoepithelial layer around the apocrine epithelium. Apocrine epithelium can occur not only in sclerosing adenosis, but in radial scars and also in ductal adenomas. Apocrine adenosis was found in 3% of consecutive series of breast biopsies for benign disease and atypical hyperplasia. Microcalcifications were twice as common in these cases as in cases lacking apocrine adenosis.[15] The lobulocentricity of sclerosing adenosis in general including involvement with apocrine change is also helpful.

We have also seen apocrine DCIS develop in pre-existing papillomas. The fibrovascular background is maintained, but both the epithelial and myoepithelial layer of the papilloma is replaced by apocrine epithelium. The apocrine cells may be only one or two cells thick or may form broad bands. The significance of focal DCIS in papillomas is unknown. We assume that there is replacement of the normal epithelium (i.e., the papillomatous epithelium) by DCIS. This would be analogous to replacement of normal epithelium in small ducts by DCIS. Certainly, in small ducts there may be involvement of only a sector or a small segment as the most minimal amount of disease. Presumably the foci of DCIS in papillomas are analogous to this. The intracystic carcinomas occasionally have a small remnant of papilloma and probably represent the most extreme transformation of papilloma to papillary DCIS whether or not it has apocrine features.

**Invasive Apocrine Carcinoma.** Deciding what constitutes invasive apocrine carcinoma

may be arbitrary to a certain extent. One can take the proteins that have been isolated from gross cystic disease fluid (GCDFP), which is produced by apocrine metaplastic cells lining cysts, and use them as markers. Of the three proteins thus isolated (GCDFP-44,-25,-15), the latter has been most extensively investigated by immunohistochemistry.[17] In a large retrospective study of 562 patients with infiltrating carcinoma, 55% stained with GCDFP-15. Of the 334 cases histologically judged to have apocrine features, 75% demonstrated positivity. On the other hand, 205 cases judged to be nonapocrine by hematoxylin and eosin criteria, only 23% had positive staining. Thus, there is a trend, but obviously not uniformity in judging what constitutes apocrine "differentiation" as measured by this particular criterion.[7]

In the study alluded to above, patients with positive staining for GCDFP-15 did not show a different outcome stage for stage than patients lacking the stain.[5,7] This fits with the earlier study by Frable and Kay who demonstrated that infiltrating carcinomas with apocrine features did not behave differently, a conclusion also reached by Abati et al.[1,4]

This logically raises the question as to why one would bother to identify carcinomas with apocrine features. One potential reason is that there may be a unique response to the administration of androgen (specifically Halotestin). In a study by Miller et al. on 120 breast cancer explants, apocrine morphology correlated with the amount of GCDFP-15 released by the breast cancers, and the presence of androgen receptors but not estrogen receptors.[8] It appears the estrogens repress the rate of production while stimulating cell growth.[13] Conversely, androgens stimulate production of GCDFP-15 but slow division activity.[14]

Clinical data indicate that Halotestin will also result in an increase in serum GCDFP-15 levels.[5] The anti-tumorigenic effect remains to be evaluated.

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# CASE #18

**Ductal Carcinoma In Situ - Multiple Types**

**General Considerations**

The purpose of the microscopic diagnosis of ductal carcinoma in situ (DCIS) is to identify the patient who is at the highest risk for the subsequent development of invasive cancer when compared to other microscopic images. It does not mean that every untreated case diagnosed as DCIS will become invasive cancer. Nevertheless, we are certain that one form of DCIS has a high rate of subsequent invasive carcinoma if not treated. It is the cancer with a large, pleomorphic cell population usually accompanied with necrosis; the prototypical "comedocarcinoma" as we have traditionally used that term. The syllable "comedo" simply means that there is necrosis, and it does not take into account either the cytology or the architecture of the cells. To be sure, many "traditional" comedocarcinomas have large pleomorphic cell populations, but this is not always the case For instance, a uniform small cell cribriform DCIS may have extensive necrosis and to call that "comedocarcinoma" could lead to totally inappropriate excessive therapy. The rubric "comedocarcinoma" is progressively being abandoned as a specific diagnosis.[3,10,11]

As stated above, the value of diagnosing ductal carcinoma in situ (DCIS) is to identify a patient who is at the maximum risk for developing invasive carcinoma if no further therapy is carried out. In one series, this risk was 10x or 11x that of the population in general for non-necrotic cribriform or micropapillary DCIS.[18] It is the same relative risk as shown in patients with untreated lobular carcinoma in situ (LCIS). Relative risk is derived by taking the number of patients with untreated DCIS who develop invasive cancer and dividing that by the number of age-matched patients actually found to have invasive carcinoma in the population at large with the same duration of follow-up. Page et al. found that 28% of patients with micropapillary/cribriform DCIS developed invasive carcinoma during an average 16 year follow-up.[18] This is a 10x or 11x relative risk compared to a woman in the general population of the same age followed for the same length of time.

<u>Microscopic Features on Your Slide.</u> This is an exceedingly variegated lesion that can be broken into several components. These include adenomyoepitheliomatous proliferations, papillomas with cytologic atypia, ducts with sieve-like and/or irregular cribriform carcinoma, clinging carcinoma, and the presence of cytologically abnormal cells confined to "resting" and unfolding lobules. In addition, portions of lobules (that are otherwise populated by normal cells) have dilated ductules lined by cells with enlarged basally oriented nuclei.

The adenomyoepitheliomatous proliferations have cytologically benign epithelium lining fibrovascular stalks that are rich in myoepithelial cells. An occasional myoepithelial cell is in mitosis As far as I am concerned, this is a coincidental finding.

Some papillomas on your slide have well-defined fibrovascular stalks with an occasional sector still lined by uniform small cells with elongated nuclei seen in typical, benign papillomas. However, a totally different population of cells with broad, vesicular nuclei line most of the papillae. The cells are irregularly spaced, and the nuclei are often closely packed together indicating a high nuclear-cytoplasmic ratio. Moreover, there is necrotic cytoplasm and nuclear debris in a few ducts.

In other foci, many expanding ductules or unfolding lobules are closely approximated to one another and are almost indistinguishable from a papilloma because the individual ductules are surrounded and separated by thin fibrovascular strands. These strands are the residual intralobular stromal and vascular components rather than newly proliferated intraluminal stalks that occur in true papillomas. We have seen several cases in which epithelial proliferations resembled a solitary intraductal papilloma at low power. However, they lacked a circumferential duct wall, and fibrous septa interrupted the nests of epithelium. We believe that these are unfolding lobules that have an epithelial proliferation similar to that seen in your sections, In our study, the tumor formed a solitary mass, and we referred to them as "solitary mass due to unfolding lobules with papillomas" (SMULP).[14] The importance of separating SMULP from papilloma is that the

database dealing with patients with true papilloma should not be applied to these lesions that are mimics of papilloma. Their biologic significance (if any) is unknown at this time.

Another image on your slide consists of ducts lined by abnormal cells three to five cells in thickness. The vesicular nuclei, the crowding, and the lack of orientation separate these from normal cells or the cells of ordinary hyperplasia. Their appearance raises the diagnosis of clinging carcinoma (CC). Clinging carcinoma has received little attention in the literature since Azzopardi first described it in his book in 1979.[2] Eusebi et al. have recently included several patterns under CC, many of which would be diagnosed by others as micropapillary or cribriform carcinoma.[7] They consider the latter as CC when the papillations or Roman bridges are confined to the periphery of the duct. Another type of CC has a proliferation of abnormal cells forming a layer three to five cells in thickness. In their study, the cases of CC were divided into two groups. One group had only a flat layer, and the other had a flat layer with an additional component of micropapillary proliferation. None of the patients with a pure flat layer had subsequent disease during a follow-up period that ranged from 15 to 25 years (median 19 years). This brings up the appropriateness of calling CC a carcinoma.

Three patients with combined flat and micropapillary carcinoma developed invasive ductal carcinoma 6, 6, and 11 years later. In two patients, the cancer was in the site of the original biopsy, whereas in one patient, the carcinoma was in the opposite breast. All three patients died of disease. It is highly pertinent that in all three patients the nuclear grade of the DCIS was high grade pleomorphic. It is also of interest that the relative risk for developing cancer was 1, indicating that these cases did not exceed the number expected in the population at large.[7]

In other areas from your case, individual ductules have cells with scant cytoplasm and fairly uniform nuclei. These appear to be a monomorphic population of cells which has been considered a criterion for DCIS for many years. Moreover, the architecture of these foci corresponds to "rigid bridges" and "Roman bridges" in some areas. In other areas there is a sieve-like pattern with well-formed lumens and cells having a good orientation to the lumen. The elegant three-dimensional studies of Ohuchi et al. indicate that these are completely enclosed spheres.[17] Therefore, there is a double layer of nuclei between each of the spaces. This is an excellent criterion to assist in recognizing this particular pattern as DCIS in contrast with the residual, passively formed spaces of ordinary hyperplasia. The studies by Ohuchi et al. and Faverly et al.[8,17] show that DCIS may be a localized process.

**Interobserver Variability in Diagnosis of DCIS.** The interobserver variability of DCIS has been a subject of much conversation, and it has been an issue in medical malpractice cases in which the pathologic diagnosis has been in question. Rosai sent glass slides to five pathologists with special interest in mammary pathology.[19] Each slide had a small area circled in ink and the pathologist was given the choice of making the diagnosis of usual hyperplasia, atypical hyperplasia, or carcinoma in situ. In only three cases (18%) did four of five pathologists agree on the exact category, and in only nine cases (53%) did three of five pathologists agree. Moreover, six cases (35%) had diagnoses that spanned the spectrum from usual hyperplasia, atypical hyperplasia and CIS. To top it off, two of the pathologists were polarized. One pathologist called every lesion atypical hyperplasia or CIS and the other pathologist never diagnosed CIS and considered only four as atypical!!!

Schnitt and coworkers organized a similar study using 24 slides of ductal proliferations with a single small area visible on a slide that was otherwise covered with masking tape.[21] In contrast to the Rosai study, the six participating pathologists (three of whom had been in the Rosai study) were given narrative and diagrammatic information regarding the criteria of Page. Page circulated 15 tissue slides diagnosed as usual hyperplasia, atypical hyperplasia or noncomedo DCIS for review. After this preparation, the study slides were sent out. All six pathologists agreed on the diagnosis in 14 (58%) of the 24 cases. Five of six pathologists agreed in 17 (71%) of cases, and four of six pathologists agreed in 22 (92%). The majority

of discrepancies were between atypical hyperplasia and DCIS. Only two cases covered the spectrum of usual hyperplasia, atypical hyperplasia and DCIS. Furthermore, and this is of great importance, no pathologist was more "malignant" or "benign" as measured by kappa analysis. Although there was not perfect consensus on every case, this study certainly demonstrates that a higher degree of reproducibility can be attained when standardized criteria are applied. It is also important to realize that the cases selected by Schnitt and coworkers for their study were selected because of their morphologic complexity and unusual appearance. They did not represent 24 consecutive breast biopsies accessioned as day to day specimens. In this latter, real life scenario, it is likely that there would have been complete agreement among all experts including the practicing pathologist in at least 90% (and probably 95%) of cases.

**INTEROBSERVER VARIABILITY ON DUCTAL LESIONS. AGREEMENT AS TO WHETHER HYPERPLASIA, ATYPICAL HYPERPLASIA, OR DUCTAL CARCINOMA IN SITU**

| Standardized Criteria[21] (24 cases) (6 pathologists) | | No Standardized Criteria[19] (10 cases) (5 pathologists) | |
|---|---|---|---|
| No. of Pathologists in Exact Agreement | Cases (%) | No. of Pathologists In Exact Agreement | Cases (%) |
| 6 of 6 | 58 | 5 of 5 | 0 |
| 5 of 6 | 71 | 4 of 5 | 20 |
| 4 of 6 | 92 | 3 of 5 | 50 |

## Conservative Therapy - The Lagios Experience.

Lagios and colleagues have been following women with DCIS treated only with tylectomy.[12] They divided their cases into four subtypes using a combination of cytologic and architectural features. Type I has large pleomorphic cells in solid sheets usually accompanied with a large central area of necrosis. Type II has an irregular papillary or cribriform pattern consisting of less pleomorphic cells associated with a central area of necrosis. Type III consists of smaller cells with mild pleomorphism. Necrosis, if present at all, is only in minute foci. Type IV is DCIS with small, uniform cells in a cribriform or micropapillary pattern and lacking necrosis.

The patients of Lagios et al. have been followed for a variable period with eight of the 79 developing subsequent DCIS or invasive carcinoma. All new lesions have been ipsilateral. Correlation of type and recurrence is below. Meyer has shown that the type IV DCIS has a low thymidine labeling index, whereas type I DCIS is high.[15] Therefore, there is good correlation of histology and kinetics.

**DCIS - Recurrence after Local Excision Alone**
**(Original Lesion <2.5 cm)**

| Subtype | | No. | Recurrent | % |
|---|---|---|---|---|
| I | Comedo (solid) | 31 | 5 | 16 |
| II | Comedo (glands) | 5 | 2 | 40 |
| III | Cribriform (high grade) | 10 | 1 | 10 |
| IV | Cribriform (low grade)* | 33 | 0 | 0 |
| | | **79** | **8**** | **10%** |

* Includes micropapillary
** 4 DCIS 4 Invasive

Lagios et al. Cancer 63:618, 1989

Patients who have DCIS presenting with a palpable mass have been treated by lumpectomy followed with XRT. In one series, patients with a comedocarcinoma component had a high rate of local recurrence (16%), whereas 28 patients with pure cribriform or micropapillary small cell carcinomas had no recurrence.[11] It is interesting that this recurrence rate is very similar to the recurrence rate of impalpable mammographic detected DCIS as illustrated in the above Table.

**DCIS In Autopsy Studies.** Recent autopsy studies show that a surprisingly high percentage of women without a previous history of breast disease have so-called in-situ cancers. Alpers and Wellings found that 6% of women have DCIS,[1] and the study by Nielsen et al. showed that 14 (18%) of 77 consecutive autopsied women had DCIS, LCIS, or both.[16]

It is therefore not surprising that there should be an appreciable yield of these lesions on mammographic generated biopsies. The crucial issue is how many of these so-called in situ "cancers" are of any biological importance as opposed to those that are of no importance to the majority of women. This will remain unanswerable until it is possible to identify a truly malignant cell (transformed cell) and distinguish it from a morphologically identical benign cell. The stain for a "cancer cell" does not exist.[9]

**Quantification Of DCIS.** A frustrating situation is to find only one duct showing classical DCIS of noncomedo type. It is unfortunate to label a patient as having carcinoma in situ with such minimal disease. There are two ways around this. One is to use the criterion of Page et al. who require that at least two ducts be completely and unequivocally involved.[18] The other is to use the criterion of Tavassoli and Norris.[23] They require that the diameters of the involved ducts be greater than 2 mm in the aggregate. Anything less than this is called atypical hyperplasia. The follow-up on their patients with qualitatively diagnostic DCIS with less than 2 mm of involvement indicates that the risk for invasion is only 9% (as opposed to ordinary hyperplasia where the risk of invasion is 5%). The studies by Dupont and Page, however, showed that atypical hyperplasia with a positive family history for breast cancer raises the risk for subsequent cancer almost as high as patients who have the full criteria for DCIS.[6]

The treatment of DCIS with lumpectomy and radiation therapy has been followed with recurrence rates ranging from 6-20%. Using current techniques of pathology examination of margins, tumor recurrence is probably in the range of 10%. Approximately 50% of recurrences are invasive, and, at least 50% of these invasive lesions can be salvaged with mastectomy. Thus, the risk of breast cancer mortality is in the range of 2% to 3% for patients treated for DCIS with lumpectomy and radiation.[5,22] Undoubtedly, there will be a greater risk as years go by and patients are at risk for longer periods of time with this recently introduced technique.

The risk of developing invasive contralateral breast cancer also exists in patients with DCIS.[24]

| RISK FOR INVASIVE CANCER IN PREMAMMOGRAPHY ERA | | REFERENCE |
|---|---|---|
| Lobular "carcinoma in situ" | 30% | 20 |
| Non-comedo DCIS | 28% | 18 |
| Atypical hyperplasia (+ Fam. Hx) | 25% | 6 |
| Atypical hyperplasia (No Fam. Hx) | 10% | 6 |
| Hyperplasia (no atypia) | 4% | 6 |
| No hyperplasia | 2% | 6 |

**The Association of "Biological Markers" with DCIS.** A number of studies have correlated the presence of p53, cerb$B_2$, estrogen and progesterone receptors, and Ki-67.[4,25] Not surprisingly, the cytologically high grade level tumors have high expression of cerb$B_2$ and p53 as well as considerable proliferative activity as measured by Ki-67. Estrogen and progesterone receptors tend to be absent. The converse is true for well-differentiated tumors, with intermediate tumors falling in between. The diagnostic utility of these observations is thus far nil, and whether there will be prognostic ramifications remains to be determined.

**Histologic Correlation of Infiltrating Cancer and DCIS.** Lampejo et al. have attempted to evaluate the clinical relevance of DCIS vis-à-vis invasive carcinoma.[13] They looked at 215 cases of infiltrating carcinoma that also contained DCIS. Only 14 (7%) of their cases had low grade DCIS. Most (11 of 14) of the invasive carcinomas were grade I and the remaining three were grade II. Overall findings are summarized below.

| DCIS Type* | | Invasive Cancer Grade* | | |
|---|---|---|---|---|
| | | I | II | III |
| 14 | Low grade | 11 | 3 | 0 |
| 52 | Intermediate grade | 9 | 41 | 2 |
| 149 | High grade | 3 | 73 | 73 |
| 215 cases | | | | |

* All numbers are numbers of cases

The fact that there is such a small number of low grade DCIS compared to its large proportion in mammographically detected DCIS may well indicate that a small number of this type of DCIS ever evolves into carcinoma. (This has already been shown by Lagios *vide supra.*) This is further reason to subdivide DCIS and to follow these patients for a very long time period.

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## CASE #19

**Spindle Cell Carcinoma**

Spindle cell proliferations of the breast include two major categories. One group lacks an epithelial component including nodular fasciitis, aggressive fibromatosis, myofibroblastoma, and sarcomas (e.g., fibrosarcoma or malignant fibrous histiocytoma). These are not discussed further. The second group has a spindle cell element combined with epithelium. This broad definition includes cystosarcoma phyllodes and metaplastic carcinoma (sarcomatoid carcinoma). Realistically, cystosarcoma phyllodes does not enter into the differential and is described in the next section.

The term metaplastic carcinoma has been used for neoplasms of the breast containing a malignant epithelial element and a malignant stromal element that may either be nonspecific (spindle cells without further differentiation) or heterologous elements such as cartilage, bone, striated muscle, or fat. It is a very heterogeneous group. The assumption has been made that epithelial cells differentiate into the mesenchymal elements, i.e., "neoplastic metaplasia." This is an outdated concept. Another problem that has existed is to refer to breast neoplasms are carcinosarcomas. The therapy may well end up being directed at the "sarcoma" component of the diagnosis, and the utility of this term seems to have run its course.

In order to get around conceptual and potentially therapeutically harmful problems, the term sarcomatoid carcinoma has gained favor. This term presumes that a totipotential stem cell gives rise to both an epithelial population and a "mesenchymal" population of cells. This has been articulated well by Wick and Swanson[10] and it has been expanded upon by Foschini et al.[2] dealing specifically with biphasic tumors of the breast. The value of the term sarcomatoid carcinoma is to focus on the concept of divergent differentiation of the neoplastic stem cell.

The usefulness of any diagnosis depends on the availability of a pertinent literature giving information regarding therapy and prognosis regardless of the terminology. Spindle cell carcinoma with the constellation of findings seen in this case was well described in 1981 by Gersell and Katzenstein.[3] They provided ultrastructural evidence of squamous differentiation of the spindle cells. Bauer et al. presented four additional cases in 1984,[1] and in 1989, Wargotz et al. reported 100 cases of spindle cell carcinoma with follow-up.[9] Diagnosing our case as spindle cell carcinoma makes it congruent with the terminology used in the above papers because it has the features that are identical to the morphologic congeries of changes described in these papers. One can use these reports for prognostic purposes thereby.

**Microscopic Findings.** The tumor has a spindle cell background with minimal nuclear atypia. Mitoses average 2/10 HPF. The spindle cell component is focally storiform and in other areas has a more meandering configuration. Three different epithelial elements are irregularly distributed within this fibrous background. The most conspicuous epithelium is mature, completely cytologically normal squamous epithelium. It frequently shows small extensions of cells into the adjacent spindle cell component where they blend imperceptibly. In other areas, the squamous epithelium partly or totally lines small, irregularly shaped spaces sometimes only forming a single layer of cells. At first glance they appear to be vascular spaces, but they do not contain blood.

The second epithelial component consists of sparse glands in which the epithelium appears jumbled. The nuclei are "active" and occasionally mitoses are seen. A distinct myoepithelial layer is not evident either by H&E or on immunohistochemical staining. The possibility that these might be entrapped ductules is unlikely because the glands are widely scattered, and there is no indication that they are related to terminal duct lobular units or adjacent larger ducts near lobules. A third epithelial element has an irregular epithelial proliferation frequently associated with hyalinized stroma immediately beneath or intermixed with the epithelium. At first glance these appear to be papillomas. However, their irregular shape and widely scattered distribution makes this type of change appear to be part of the tumor. On some of the sections, a true papilloma is present in a duct measuring approximately 3 mm in diameter, which is

viewed as a coincidental finding.

The spindle cell component is focally positive for S-100 and muscle-specific actin. Although only a small percent of the cells stain, they are clearly neoplastic based on the placement of the cells and their abnormal nuclei. Wargotz et al. noted similar staining in some of the spindle cells in their series.[8] These cells can be viewed as differentiating towards myoepithelium or myofibroblasts. Epithelial markers in the spindle cell component has been clearly documented in another study.[6]

## DIFFERENTIAL DIAGNOSIS

The only lesion that might be considered under the differential diagnosis would be an infiltrating myoepithelial carcinoma. Because of the immunohistochemical staining of the spindle cells suggesting myoepithelial differentiation, myoepithelial carcinoma could be considered. These lesions, however, lack well-formed glandular or squamous elements. Only five cases of myoepithelial carcinoma have been reported, one of which metastasized.[7] We have seen one case of infiltrating myoepithelioma that had rounded epithelial-like cells arranged in solid aggregates that blended with the spindle cell component. They were not a discrete component, nor did they make a lumen. From an immunophenotypical standpoint, both the round and spindle cells were a single population.

**Prognosis.** Fifty-six of the 100 patients of Wargotz et al. with follow-up had recurrence.[8] Local recurrence or metastases occurred three weeks to 11 years after diagnosis with a median of one year. Forty-seven patients had nodal dissection and three (6%) had positive nodes. The most common course of events was local recurrence followed by metastasis to pleura and lungs. Metastases to bone and other sites occurred late in the disease. Of the 56 patients with recurrence, 44 (79%) died of disease. Twenty-nine of the 30 with distant metastases died of cancer, and five of 17 with local recurrence died of cancer; presumably due to uncontrolled local growth.

The initial therapy consisted of local excision only (78%). Eventually 38% of patients had partial mastectomy, 56% had simple mastectomy, and 46% had radical mastectomy or modified mastectomy. Radiation therapy or chemotherapy was given in eight patients, and six of these eight patients died of disease.

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## CASE #20

**Malignant Phyllodes Tumor**

Phyllodes is the Greek word for leaf and refers to the irregular stromal protrusions into the ducts. The term phylloides may also be used. One of these words is singular and one is plural, although I am unsure which is which (having been told both ways).

The definition of a phyllodes tumor (PT) requires that there be (1) stromal hypercellularity and (2) a leaf-like configuration to the epithelial lined spaces. The stromal hypercellularity **must** resemble a low grade fibrosarcoma, although it may be seen only in a few foci. In many areas, the cellularity often does not exceed that of an ordinary fibroadenoma, and broad areas of almost acellular collagen are common. Stromal hypercellularity can be accentuated beneath the epithelium, but often the stroma is sparsely cellular beneath the epithelium. In short, the oft-quoted "criterion" of perlepithelial dense stromal cellularity is unreliable. Areas of paucicellular myxoid stroma are common. The stromal cells are fibroblasts and myofibroblasts.[2]

Dividing PT into low-grade, borderline, and malignant categories has some merit, although it is never prognostically applicable to an individual patient with 100% certainty. The classification is made in the area of greatest stromal cellularity and mitotic activity. The low grade group has four or less mitoses per 10 HPF, the borderline group has five to 10 mitoses per 10 HPF, and the malignant group has greater than 10 per 10 HPF. The borderline group is important because these rarely if ever metastasize and in common with the low grade category, are only at risk for local recurrence.

Malignant PT with mitotic counts exceeding 10 per 10 HPF are usually characterized by dense cellularity and marked pleomorphism with bizarre cells. Moreover, there is usually stromal overgrowth, which is defined as one low power field of stroma lacking epithelium. (This is based on a low power field with a 10x widefield eyepiece and 40x objective.) The term stromal overgrowth was used in 1954 in a paper by Lester and Stout[11] and is emphasized as a feature seen in most metastasizing tumors by Ward and Evans.[18] In the case available to you, bizarre cells are not present. There is a modest degree of pleomorphism with enlarged, vesicular nuclei. The designation of malignant phyllodes tumor is based on the mitotic count that exceeds 10 per 10 HPF.

The death rate from PT is undoubtedly exaggerated, because most reports stem from referral institutions. For instance, in the study by Ward and Evans from M.D. Anderson Hospital, seven of 26 patients died.[18] In my own literature review of multiple series in which tumors have been divided into benign, borderline, and malignant categories, only about 4% of tumors metastasize. All of these tumors are in the malignant group, but only about 15% of "malignant" tumors metastasized.

Multiple parameters have been investigated in an effort to prognosticate. Patient age, tumor size, necrosis, mitoses, stromal overgrowth, pleomorphism, and the quality of the margin (pushing vs. circumscribed) have been analyzed. There is a trend in most metastasizing tumors to have many of the above features. High mitotic count, stromal overgrowth, infiltrating margin, tumors greater than 4 or 5 cm, patients older than 60 years, and the presence of heterologous sarcoma (liposarcoma or osteosarcoma) are markers of metastasizing lesions. Nevertheless, there are exceptions to every rule.

The use of flow cytometric data has been inconsistent (see table below). In the study by El-Naggar et al, no patient with diploid tumors developed metastases, whereas all but 3 of 12 patients with aneuploid tumors had metastases.[5] On the other hand, Palko et al. found no correlation between tumor ploidy and clinical outcome. However, they showed that an S-phase >5% correlated with metastases. These and one other study failed to find correlation between clinicopathologic features and flow cytometric data.[10]

**FLOW CYTOMETRIC DATA**

| | S - PHASE | PLOIDY |
|---|---|---|
| Ref. 1 | >5%<br>3/5 metastasized.<br><5%<br>1/8 metastasized. | Diploid - 2/12 metastasized.<br>Aneuploid - 2/3 metastasized. |
| Ref. 2 | ≥5%<br>10/17 recurred.<br><5%<br>1/12 recurred. | Diploid - 0/17 metastasized.<br>Aneuploid - 9/12 metastasized. |

1. Palko et al. Arch Pathol Lab Med 115:949, 1990
2. El-Naggar et al. Am J Clin Pathol 93:480, 1990

Suffice it to say, there are some general statements that can be made, but no single tumor respects any criterion.[4,8,12,15] A classic example is one of the metastasizing tumors reported by Norris and Taylor that was low grade, lacked mitoses, was not necrotic, had a sharply circumscribed border and measured 2 cm.[13] There is a trend, however, for some features to correlate with outcome. For example, three out of four patients over the age of 60 developed metastases in one series,[10] but this is not verified in others.[9] Tumors greater than 5 cm with an infiltrating margin and necrosis are more likely to metastasize.

Stromal overgrowth is seen in most cases with metastases (six out of seven in the study by Ward and Evans), although two other patients lacking stromal overgrowth had metastases.[14] Hawkins et al. reviewed published series and concluded that 72% of patients with stromal overgrowth developed metastases.[9]

Some patients with metastases have had local excision as the initial surgery, suffered local recurrence and then developed metastases. Nonetheless, some patients treated with mastectomy as the first therapy have had metastasis indicating that recurrence is not a requisite or a necessary step in the progression of disease. Metastases are usually to the lung and pleura only, although occasionally there is dissemination to abdominal viscera or bone. Lymph node metastases are unknown. The metastases always consist only of the sarcomatous component and may appear from six months to 10 years after the initial surgery (median time is about two years). One patient had a solitary pulmonary metastasis resected and she lived free of disease for 15 years.

**Phyllodes Tumor in Young Women.** The diagnosis of PT should be made with extreme caution before age 30. When adequately illustrated, nearly all reported cases of phyllodes tumor in this age group are giant fibroadenomas of ordinary histologic type or juvenile fibroadenomas with their characteristic focal hypercellularity. Only a few cases of metastasizing PT have occurred in adolescents or young adults.[17] Local recurrence of malignant PT in adolescents is equally rare.[1]

## DIFFERENTIAL DIAGNOSIS

Fibroadenomas are the only lesions that enter into the differential diagnosis of PT. This usually occurs when the stroma is more cellular than expected. The term cellular fibroadenoma has been used for fibroadenomas with a stroma as cellular as seen in PT. The difference lies in the architecture of the lesion. The gaping

spaces of PT are absent as well as the leaf-like shapes of stromal proliferations. To be sure, these can occasionally be seen in two or three foci, but always represent a tiny minority of the lesion. Most fibroadenomas occur in patients less than 35 year of age, whereas most PT are beyond the age of 40 years. Rarely, multinucleated cells with moderately bizarre nuclei occur in the stroma of fibroadenomas.[3] The remainder of the stroma, however, is not densely cellular, and the leaf-like pattern of stromal proliferation characteristic of PT is absent.

A separate group of fibroadenomas has been termed juvenile fibroadenoma (although the term cellular fibroadenoma is sometimes used for this group as well).[16] The lesions have stroma that may have the density of PT with an occasional focus having an irregular stromal growth producing small leaf-like projections. This is uncommon, and overall, they do not architecturally resemble PT. Juvenile fibroadenomas do, however, have one other feature similar to PT, namely a prominent epithelial proliferation. The irregular piling up of epithelium often with small micropapillary protrusions is identical in juvenile fibroadenomas as well as in most PT.

Juvenile and fibroadenomas tend to be large (mean of 5 cm) and markedly distort the breast.[16] They have also been referred to in the literature as "cellular fibroadenomas" because of the stromal hypercellularity.[7] One other term that is sometimes used is giant fibroadenoma. In the past, this has been used interchangeably with benign PT, but this is inaccurate. A giant fibroadenoma (something larger than 8-10 cm) has only the features of fibroadenoma and lacks the gross and microscopic characteristics of PT.[6]

Most juvenile fibroadenomas occur before the age of 30, but they have been reported in women as old as 70.

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