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CALIFORNIA TUMOR
TISSUE REGISTRY

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ENDOCRINE TUMORS

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Case Histories

Case 1 #27982
Multiple tan-colored nodules, ranging in size from 1.7 to 2.1 cm, were present in both lobes of the thyroid of a 26-year-old woman. Total thyroidectomy was performed

Case 2 #27005
This 33-year-old, previously healthy female presented with a four month history of a neck mass. Tc99 pertechnetate scan revealed a large, nonfunctioning nodule in the right lower pole of the thyroid. She was started on Synthroid 0.1 mg per day. Ultrasound demonstrated a 4.9 x 2.6 x 3.6 cm solid mass without cysts or calcifications. Excision of the right lobe and isthmus of the thyroid was performed, along with removal of right cervical lymph nodes. The excision specimen showed a 4.5 x 4.0 x 2.9 cm fluctuant nodule which was well circumscribed but not encapsulated.

Case 3 #28012
A 3.0 cm circumscribed nodule was found in the right lobe of the thyroid of a 64-year-old woman. A hemithyroidectomy was performed.

Case 4 #28009
This 52-year-old woman presented with a thyroid nodule. A 3.5 cm, solitary, well-circumscribed, tan-colored nodule was seen in the lobectomy specimen. The cut surface was gritty.

Case 5 #26804
This 78-year-old man presented with a painless right thyroid mass, which had been present for an undetermined time interval. Ultrasound revealed a large solid mass within the right lobe of thyroid. A right lobectomy was performed. Within the specimen was a 4 cm diameter, encapsulated, firm, pale and vaguely lobulated mass.

Case 6 #28011
A 3.5 cm encapsulated nodule was present in the right lobe of the thyroid of this 36-year-old man.

Case 7 #28010
This 67-year-old female presented with rapid enlargement of the thyroid. Total thyroidectomy was performed, which revealed a large tumor in the right lobe, measuring 7 x 6 x 6 cm. The borders were not circumscribed. There were firm, tan, solid areas as well as hemorrhagic areas.

Case 8 #17381

An otherwise asymptomatic nodule in the left lobe of thyroid of this 69-year-old female had grown rapidly for two months. Thyroid scan showed a cold nodule. A total thyroidectomy was performed with limited neck dissection on the left. The left lobe was replaced by granular, yellowish-tan material with some calcified areas.

Case 9 #26961

For five months this 67-year-old woman presented had noticed a right neck mass. The mass had increased in size rapidly over a two-month period, and became painful two weeks prior to hospitalization. The patient also complained of intermittent right neck/head/ear pain for 2 weeks. The neck mass was hard, slightly tender, and fixed at the right thyroid lobe. A neck CT scan showed a 5 cm mass in right lobe of thyroid, causing deviation of the trachea, and extending into the parapharyngeal space. Thyroidectomy and tracheostomy were performed. The specimen was received in multiple irregular fragments of firm tissue, with the largest piece measuring 6.5 cm. There were necrotic areas.

Case 10 #24795

This 25-year-old man presented with a nine month history of a right neck mass. Scanning revealed a cold nodule in the right thyroid lobe. Subtotal thyroidectomy was performed. The specimen showed an encapsulated 2.8 cm tumor which was gray-tan, red-tan to tan-yellow.

Case 11 #18440

This 59-year-old man with a previous history of testicular seminoma (18 years ago) had had an enlarged thyroid for all of his adult life. In the 6 weeks prior to hospitalization, the thyroid was noted to enlarge rather rapidly. A large cold nodule was detected in the right lobe of thyroid on a scan. Neck exploration was performed, revealing that the right lobe of thyroid was hard and adherent in one spot to the skeletal muscle. The nodule was removed. The cut surfaces showed gray to tan tumor with foci of apparent calcification.

Case 12 #28013

A right thyroid nodule was found in an 85-year-old woman. Thyroidectomy revealed a 4 x 3 x 3 cm firm, white, gritty lesion replacing the entire thyroid and extending into the surrounding tissues. Cervical lymph nodes were also enlarged.

Case 13 #28007

This 49-year-old woman presented with a right thyroid mass. Right lobectomy was performed, revealing that the right lobe was nearly totally replaced by a 9 x 7 x 5 cm well-demarcated solid, ovoid tumor with some cystic spaces.

Case 14 #20099

This 74-year-old female presented with painless enlargement of her thyroid gland of two months' duration. Examination revealed an enlarged, slightly nodular left thyroid lobe. An iodine uptake scan showed findings within normal limits. A cold nodule 4 cm was detected. Left hemithyroidectomy was performed, revealing pink-tan and lobulated tissue.

Case 15 #28008

Left thyroid enlargement was noted in this 30-year-old woman. A left hemithyroidectomy was performed. The specimen measured 5 x 4 x 3 cm, and showed ill-defined whitish firm areas.

Case 16 #26320

This 58-year-old woman presented with chronic left shoulder pain, general malaise and fatigue. There was increasing pain around her scapular areas on the left side. Routine workup showed an elevated calcium (10.9 to 11.6 mg/dl). CT scan and bone scans revealed a questionable mass consistent with parathyroid tumor. A right parathyroidectomy was performed. The specimen consisted of a single tan-brown, glistening, grossly encapsulated piece of tissue measuring 20 x 6 x 5 mm, weighing 1 gram.

Case 17 #27298

A 53-year-old man presented with 3 months' history of hoarseness. There were aches and pains all over the body, as well as tachycardia. Workup showed hypercalcemia (12.4 mg/dl). Examination revealed vocal cord paralysis on the left side. A mass was felt in the left neck. Neck exploration with excision of a large left parathyroid mass was performed. The specimen was an ovoid, gray tissue with fat attached. It weighed 24 grams, and was thinly encapsulated, measuring 3.8 cm in maximum dimension. Cut surface showed centrally scarred, slightly trabeculated, gray, uniform tumor.

Case 18 #26073

This 69-year-old man presented with vague left-sided abdominal pain for a number of weeks. A palpable mass was detected for one week. CT scan showed a large, well defined left upper abdominal mass filling the left upper quadrant, extending anteriorly against the anterior abdominal wall. Resection of the left upper abdominal tumor (encapsulated and arising from the left adrenal gland) was performed. The specimen weighed 2230 grams, and measured 20 x 16 x 12 cm. It was ovoid and completely encapsulated. The tumor had a variegated appearance, with yellow, brown, red and white areas, as well as necrosis and hemorrhage.

Case 19 #26317

During workup for prostatic symptoms, an intravenous urogram showed a mass in the adrenal of this 68-year-old man. CT scan showed a 7 cm right adrenal mass. It was removed. The 6.0 x 5.7 x 4.2 cm encapsulated specimen had thinned adrenal tissue was attached at one pole. The tumor was brightly yellow-organ, with slightly bulging, soft cut surfaces.

Case 20 #19398

This 61-year-old female presented with cyanosis and shortness of breath. She also had back pain of one week's duration. She was treated with digitalis and aminophylline. The next morning, she had left leg pain with no pulse in the femoral area. There was continued shortness of breath, and the patient succumbed the next day. At postmortem, the left adrenal gland was markedly enlarged, measuring up to 6 cm, with a central soft gray-tan mass.

Case 21 #23355

An incidental left neck mass was found during a physical examination of this 51-year-old female. Examination of the oropharynx showed a prominent bulging of the left lateral pharyngeal wall posterior to the posterior tonsillar pillar. The mass was non-tender and non-mobile. The mass was excised. The specimen was received in separate fragments, and the largest piece measured up to 5 cm.

Case 22 #25293

This 17-year-old female had a documented history of Cushing's syndrome. She had markedly elevated serum cortisol levels ranging from 40.6 to 1087 (normal 5 to 29.5), nonsuppressable by either overnight 1.0 mg Dexamethasone, overnight 8 mg Dexamethasone, or low or high dose 4-day Dexamethasone suppression. The patient seemed to have intermittent autonomous cortisol secretion. Urine ketosteroids were increased. CT scan of adrenal glands revealed marked bilateral hyperplasia. ACTH was markedly elevated in the range of 218 to 459 (normal <130). CT scan of the pituitary was normal. CT scan of the chest revealed a calcified anterior mediastinal mass, which was excised. The specimen weighed 34 grams, measuring 6 x 4 x 4 cm. The tumor was well circumscribed, and the cut surfaces were mottled with gray and purple areas.

Case 23 #21358

A 46-year-old woman presented with severe recurrent abdominal pain for 6 months, occasionally accompanied by vomiting. The symptoms became increasingly frequent. Past medical history was significant for recurrent chronic duodenal ulcer. Total gastrectomy, distal pancreatectomy and splenectomy were performed. In the specimen of the pancreas, there was a 5 cm well-circumscribed tumor composed of soft, spongy, partly hemorrhagic tissue with cystic spaces.

Case 24 #26635

An enlarging skin mass had been present for two months in the anterior medial thigh of this 69year-old female. A wide excision was performed. The skin showed an ulcerated nodular lesion measuring 2 x 2 cm.

Diagnoses

Case 1 Thyroid - Papillary carcinoma, tall cell variant, with lymph node metastasis

Case 2 Thyroid - Columnar cell carcinoma

Case 3 Thyroid - Medullary carcinoma, papillary/pseudopapillary variant

Case 4 Thyroid - Hyalinizing trabecular adenoma

Case 5 Thyroid - Follicular carcinoma with focal Hurthle cell features, minimally invasive type
[Comment: The capsular invasion may not be well seen in some slides.]

Case 6 Thyroid - Papillary carcinoma, encapsulated follicular variant

Case 7 Thyroid - Poorly differentiated (insular) carcinoma

Case 8 Thyroid - Medullary carcinoma, classical type

Case 9 Thyroid - Anaplastic (squamous cell) carcinoma, arising from a Hurthle cell neoplasm
[Comment: The Hurthle cell neoplasm component is not seen in some slides.]

Case 10 Thyroid - Medullary carcinoma, spindle cell variant

Case 11 Thyroid - Spindle epithelial tumor with thymus-like element (SETTLE)

Case 12 Thyroid - Anaplastic carcinoma, paucicellular variant

Case 13 Thyroid - Solitary fibrous tumor

Case 14 Thyroid - Low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) [extranodal marginal zone B cell lymphoma], with increased large cells, arising in a background of Hashimoto's thyroiditis

Case 15 Thyroid - Papillary carcinoma, diffuse sclerosing variant

Case 16 Parathyroid - Parathyroid adenoma

Case 17 Parathyroid - Parathyroid neoplasm of uncertain malignant potential, with an unusual spindle cell component

Case 18 Adrenal - Adrenocortical carcinoma

Case 19 Adrenal - Adrenocortical adenoma

Case 20 Adrenal - Pheochromocytoma

Case 21 Soft tissue, neck - Paraganglioma

Case 22 Thymus - Carcinoid (atypical carcinoid) with ACTH production

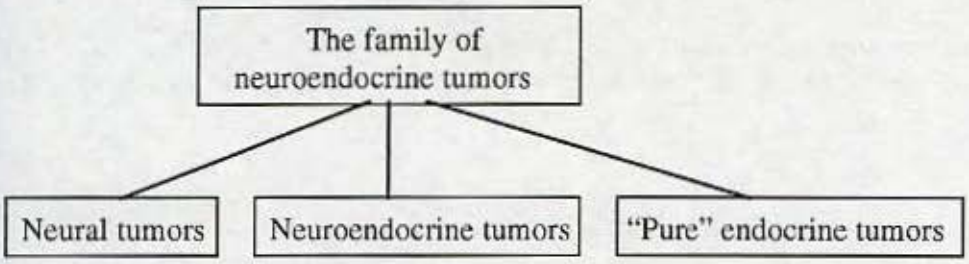
Case 23 Pancreas - Islet cell carcinoma with probable gastrin production

Case 24 Skin - Merkel cell carcinoma (small cell neuroendocrine carcinoma of skin)

A Simplified Overview of the Family of Neuroendocrine Tumors

A simplified classification of the entire family of neuroendocrine lesions will be presented here, to make it easier to understand and remember the histology, immunohistochemical profile and ultrastructural features of the diverse tumors that fall under this umbrella.

While the terms "neuroendocrine", "endocrine" and sometimes "neural" are used interchangeably in the literature and in general usage, these terms are used in a more specific sense in this presentation (as defined below), in order to aid delineation of this complicated group of tumors.



Under the umbrella of this whole family, there are three major categories:
(1) Neural tumors
(2) Neuroendocrine tumors
(3) Pure endocrine tumors

The term "family of neuroendocrine tumors" is used here to refer to all three categories.

MARKERS OF NEUROENDOCRINE CELLS

Histochemistry

The traditional method for demonstration of the neuroendocrine nature of a cell is by histochemical stains:
(1) Argentaffin reaction, such as the Masson-Fontana stain
(2) Argyrophilic reaction, such as the Grimelius stain

Immunohistochemistry
Nowadays immunohistochemistry has taken over as being the most popular technique for demonstration of neuroendocrine differentiation. If immunohistochemical studies are going to be performed anyway, it is unnecessary to perform histochemical stains (non-value-added procedures).

(1) Pan-neuroendocrine antibodies, which serve as general-purpose markers indicating the presence of neuroendocrine or neural differentiation.

(2) Specific hormones and amines, e.g. thyroglobulin, calcitonin, bombesin, insulin, ACTH; antibodies against these hormones and amines may be applied to further delineate the secretory products.

Electron microscopy
Dense-core neurosecretory granules are the hallmarks of most members of the family of neuroendocrine tumors. However, in routine practice, one rarely needs to apply this technique for diagnostic purposes.

In summary, immunohistochemistry currently represents the most important tool for the diagnosis of the family of neuroendocrine tumors.

PAN-NEUROENDOCRINE MARKERS

A number of pan-neuroendocrine markers are available.

Chromogranin
- Most specific
- However, it is not very sensitive
- Positive reaction takes the form of granular products in the cytoplasm
- Positive staining depends on the number of neurosecretory granules, i.e. unlikely to be positive if there are few granules (such as most cases of small cell carcinoma of lung)
- Thus the positivity rate approximates that of the Grimelius stain

Synaptophysin
- Fairly specific
- Highly sensitive
- In contrast to chromogranin, positive reaction is not dependent on the number of neurosecretory granules
- Positive reaction product in the cytoplasm can be diffuse or granular

Neurofilament

- A sensitive marker
- However, the paraffin section-reactive antibodies that are currently available are not very reliable and can produce false-positive reaction

Neuron-specific enolase (NSE)

- Very sensitive
- Specificity is low, even if monoclonal antibodies are used instead of polyclonal antisera
- In normal cells, NSE staining is observed only in those showing neural and neuroendocrine differentiation. However, NSE staining can be seen in a wide array of tumors, whether neuroendocrine or not, probably due to upregulation of NSE expression in a wide variety of tumors.

Leu7 (CD57)

- Limited sensitivity
- Limited specificity (also stains natural killer cells, prostatic cells, etc.)
- Not useful

In summary, the most useful markers to apply when one encounters a tumor suspected to belong to the family of neuroendocrine tumors are:

- Synaptophysin
- Chromogranin

The diagnostic value of NSE staining is very limited.

NEURAL TUMORS

Normal Tissues	Corresponding Tumors
Neurons (ganglion cells)	• Neuroblastoma • Ganglioneuroma • Ganglioneuroblastoma • Peripheral primitive neuroectodermal tumor
Adrenal medulla	• Pheochromocytoma
Paraganglion	• Paraganglioma • Olfactory neuroblastoma (Some similarity to architecture of paraganglioma, but its exact relationship with neuroblastoma versus paraganglioma remains unclear)

General features of neural tumors

- Cytokeratin: Typically negative. However, occasional cells may show positive staining when sensitive detection techniques are used. That is, the presence rare cytokeratin positive cells does not negate a diagnosis in this category.
- Pan-neuroendocrine markers: Typically positive.

That is,

1. They lack epithelial characteristics (purely neural)
2. They are rich in dense-core neurosecretory granules
3. Some such tumors may have a component of sustentacular cells (best highlighted by immunostaining for S100 protein), and they are particularly prominent in pheochromocytomas and paragangliomas

NEUROENDOCRINE TUMORS

Normal Tissues	Corresponding Tumors
Parathyroid	• Parathyroid adenoma/carcinoma
C-cells of thyroid	• Medullary thyroid carcinoma
Islet cells of pancreas	• Islet cell neoplasms
Pituitary gland	• Pituitary neoplasms
Dispersed neuroendocrine cells, e.g. gastrointestinal tract, lung	• Carcinoid • Atypical carcinoid • Large cell neuroendocrine carcinoma • Small cell neuroendocrine carcinoma
Merkel cells of skin	• Merkel cell carcinoma

General features of neuroendocrine tumors

- Cytokeratin: Typically positive; the cytokeratin is best demonstrated by using an antibody against low molecular-weight cytokeratin, such as CAM5.2. The positive reaction is either diffuse in the cytoplasm or forms a discrete paranuclear globule/dot.
- Pan-neuroendocrine markers: Typically positive.

That is,

1. They express full epithelial characteristics, such as desmosomes and cytokeratin intermediate filaments
2. They may even form glandular structures or produce mucin, as expected from their epithelial nature
3. Rich in neurosecretory dense-core granules

They are in essence "hybrid cells" with both epithelial and neural features!

PURE ENDOCRINE TUMORS

Normal Tissues	Corresponding Tumors
Thyroid follicular cells	• Thyroid follicular adenoma/carcinoma • Papillary carcinoma • Other thyroid epithelial neoplasms
Adrenal cortex	• Adrenocortical adenoma/carcinoma

General features of thyroid follicular cells

- Cytokeratin: Typically positive
- Pan-neuroendocrine markers: Typically negative
- Thyroglobulin: Positive

That is,

1. They express fully epithelial characteristics
2. They lack neurosecretory granules

General features of adrenal cortical cells

- Cytokeratin: Variable reactivity. Often positive in normal adrenal cortical cells and adrenal cortical adenomas, and often negative in adrenal cortical carcinomas, but these findings are not absolute
- Pan-neuroendocrine markers: Typically negative

That is,

1. They have no neurosecretory granules
2. They are rich in lipid and smooth endoplasmic reticulum
3. A characteristic ultrastructural finding is mitochondria with tubular rather than lamellar cristae

SUMMARY

	Cytokeratin	Pan-neuroendocrine markers
Neural tumors	-	+
Neuroendocrine tumors	+	+
Pure endocrine tumors	+	-

THE APUD CONCEPT

- The APUD (amine precursor uptake and decarboxylation) concept was first proposed in 1966
- It was a useful unifying concept:
  - ⇒ Neuroendocrine cells distributed widely over the body share similar biochemical and ultrastructural features
  - ⇒ Tumors are often called APUDomas
  - ⇒ This concept can help to explain the multiple endocrine neoplasia syndromes well
- However, this original concept also proposed that all neuroendocrine cells are derived from the neural crest (neuroectoderm)
- There is ample evidence against the "neural crest origin" postulation:
  - ⇒ Most neuroendocrine cells (at least for the gut, pancreas and lung) are of endodermal origin
  - ⇒ Not all tumors elaborating peptide hormones are of neuroendocrine origin (ectopic hormone production)
  - ⇒ Occurrence of mixed adenocarcinoma-endocrine cell neoplasms is inconsistent with this theory
- Thus, the APUD concept has to be revised, discarding the postulation on the neural crest origin

HISTOLOGIC FEATURES IN COMMON FOR THE FAMILY OF NEUROENDOCRINE TUMORS

Identification of the following histologic features should help in recognition of this group of tumors:

1. Usually growing in the form of packets and trabeculae (But trabeculae are extremely uncommon among the neural tumors)
2. Usually composed of fairly uniform polygonal cells, although there may be isolated cells with pleomorphic nuclei
3. May show nuclear palisading at the periphery of cellular islands
4. Round or oval nuclei, typically with stippled chromatin
5. Granular cytoplasm
6. Traversed by delicate fibrovascular septa or sinusoids (a "logical" finding since the tumor requires an elaborate vasculature to carry away the hormonal products)
7. May have amyloid deposits (often composed of the prohormones or the hormones themselves)

The vascular patterns in the family of neuroendocrine tumors

The two major patterns are: delicate fibrovascular septa and sinusoids. They type of vasculature often differs in different tumor types. Therefore the vascular pattern may also aid in the diagnosis, although these two patterns are not mutually exclusive, and there can always be exceptions to the lists below.

Prominent delicate fibrovascular septa

Since the blood vessels are supported by delicate fibrous stroma, they can be readily appreciated even on low magnification. They are particularly prominent in:

- Neural tumors, e.g. neuroblastoma, paraganglioma
- Most neuroendocrine tumors, e.g. carcinoid, medullary thyroid carcinoma

Sinusoidal pattern

The sinusoidal pattern differs in that it is often inconspicuous and not striking to the eye, because the blood vessels are not supported by a fibrous stroma. They are particularly common in:

- Endocrine tumors, e.g. follicular adenoma/carcinoma, adrenal cortical adenoma/carcinoma
- Parathyroid adenoma/carcinoma

PROBLEMS IN ASSESSMENT OF THE FAMILY OF NEUROENDOCRINE LESIONS

Distinction between nodular hyperplasia and adenoma can be very difficult

- Endocrine or neuroendocrine tissues showing hyperplasia often proceed from a diffuse phase to a nodular phase
- Although the distinction between nodular hyperplasia and adenoma can sometimes be easy, the distinction on some occasions can be very difficult indeed (especially in small biopsies)
- The dividing line between the two is not always sharp and clear
- In general, adenoma is *single*, while hyperplastic nodules are often *multiple*
- Nonetheless, true adenoma may also supervene on a background of nodular hyperplasia, further complicating the issue

Distinction between benign and malignant neoplasm can be difficult

The scenario

- Bland-looking tumors in the family of neuroendocrine tumors can sometimes metastasize.
- Some tumors with bizarre cells or showing significant cellular atypia may pursue a totally benign course.
- In endocrine/neuroendocrine neoplasms, cellular atypia is usually more a reflection of hyperactivity or hyperstimulation rather than malignant biologic potential.
- Aneuploidy, a characteristic feature of malignant neoplasms, can be found in some hyperplastic lesions and benign neoplasms of endocrine/neuroendocrine tissues.
- A benign endocrine/neuroendocrine tumor can kill because of its metabolic complications! Thus mortality is possible even for tumors that are biologically totally benign.
- The malignant neoplasms of endocrine/neuroendocrine organs (perhaps with the exception of adrenocortical carcinoma) are usually indolent neoplasms; thus short-term follow-up does not accurate reflect their true malignant potential.

Criteria of malignancy

- The only absolute criterion of malignancy is presence of metastasis, although absence of this feature does not exclude this possibility.
- The criteria of malignancy vary from tumor type to tumor type, and from organ to organ.
- Invasion (capsular invasion or vascular invasion) is often considered a histologic criterion of malignancy, but there are many inherent problems in assessing invasion. In particular, vascular invasion can be difficult to assess due to the high vascularity of the tumor.

Other problems of endocrine/neuroendocrine tumors

- Multiple hormones may be produced by a tumor; even a single tumor cell can produce multiple hormones.
- Multicentric disease can occur: it can be difficult to distinguish between multicentric disease and metastasis.
- Some patients may develop multiple endocrine tumors, such as the multiple endocrine neoplasia syndromes. The tumors may appear synchronously or metachronously.

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Papillary Lesions of the Thyroid Gland (Cases 1 - 3)

PAPILLARY LESIONS OF THE THYROID GLAND

Many different tumors and hyperplastic lesions of the thyroid gland can produce a papillary pattern. Assessment should include:

1. Circumscribed (can be benign or malignant) versus invasive (almost invariably malignant neoplasms)
2. Overall architectural features
3. Cytologic features

Circumscribed papillary lesions

- Nodular goiter (colloid nodule)
- Follicular adenoma with papillae
- Papillary thyroid carcinoma
- Other tumors, e.g. columnar cell carcinoma, medullary carcinoma

Invasive papillary lesions

- Papillary thyroid carcinoma
- Columnar cell carcinoma
- Medullary carcinoma, papillary variant

The commonest causes are:

1. Nodular goiter
2. Papillary thyroid carcinoma

Other non-tumorous thyroid lesions with papillae

- Thyrotoxicosis
- Hashimoto's thyroiditis

* Their papillae are typically short and stubby, and almost never arborizing

CASE 1

Salient histologic features

- The histologic sections are in fact taken from the cervical lymph nodes rather than from the thyroid itself, and residual nodal architecture can be identified at the periphery.
- The histologic features show the prototypic features of papillary carcinoma, with a mixture of papillary and follicular structures.
- The cytologic features are also characteristic.

Diagnosis

Thyroid -- **Papillary carcinoma, with cervical lymph node metastasis**

Papillary thyroid carcinoma: Definition

- A tumor showing evidence of follicular cell differentiation.
- Typically exhibits papillary and follicular structures. (The proportion of these two components varies greatly form case to case. One rarely ever sees a case that is purely papillary; some neoplastic follicles are almost always seen as well.)
- Characteristic nuclear features:
  - ◊ Ground-glass or pale (sometimes called Orphan-Annie nuclei)
  - ◊ Large size
  - ◊ Irregular outline, with deep grooves and nuclear pseudoinclusions

Papillary thyroid carcinoma: The essence of diagnosis

- Diagnosis is based mostly on nuclear characteristics (i.e. it is possible to make a definitive diagnosis even in cytologic preparations)
- It is not necessary to identify capsular or vascular invasion for this diagnosis to be made.
- A diagnosis of papillary carcinoma is usually straight-forward for tumors with a prominent arborizing papillary architecture.
- Problems in diagnosis stem from the fact that the nuclear characteristics may not be well developed in some papillary carcinomas, while nuclear clearing may occur with suboptimal fixation in a wide variety of lesions.

Distinction between papillary carcinoma and nodular goiter/follicular adenoma with papillae

The distinction should not be difficult in most circumstances if attention is paid to the architectural features and cytology.

Papillary carcinoma	**Nodular goiter / Adenoma with papillae**
Usually more delicate papillae	Follicles are often present in the cores of the papillae
Cells are often cuboidal	Cells are often columnar
Nuclei appear "up and down", a manifestation of nuclear crowding and lack of polarity	Nuclei are regularly aligned at the base of the cells
Other nuclear features of papillary carcinoma evident, e.g. clear nuclei, grooves, pseudoinclusions	Dark round nuclei

Pathologist's role in rendering a diagnosis of papillary carcinoma

1. Making a correct diagnosis
2. Is it a variant of papillary carcinoma with prognostic implications?
3. What are the prognostic factors?

Papillary carcinoma variants with prognostic significance

There are numerous morphologic variants of papillary carcinoma, but most behave no differently from the conventional form of papillary carcinoma.

Variants with better prognosis	Variants with worse prognosis
• Encapsulated variant • Microcarcinoma (<1 cm) • Latent carcinoma (incidentally found small tumors)	• Tall cell variant • Diffuse follicular variant • Diffuse sclerosing variant (?) • Trabecular variant (?) • Dedifferentiated papillary carcinoma (papillary carcinoma associated with a component of anaplastic carcinoma)

Although the diffuse sclerosing variant is associated with a higher risk of metastasis, the overall survival does not appear to be inferior to that of conventional papillary carcinoma. The unfavorable prognostic implication of the trabecular variant awaits confirmation by further studies.

Tall cell variant of papillary carcinoma

Case 1 shows features of the tall cell variant.

Morphology

- Definition of tall cell variant: Presence of over 30-70% tumors cells with height more than twice the width. Different studies have adopted different percentage criteria in their definition of this variant.
- The nuclear features should be no different from those of conventional papillary carcinoma.
- However, the cytoplasm is almost always oncocytic, and cell borders are often distinct.
- In addition, the tall cell variant is often highly papillary in architecture.

Clinical aspects

Clinically, the tall cell variant, as a group, does show some features that differ from conventional papillary carcinoma:

- Slightly older age group
- Often a bulky tumor
- Frequent extrathyroidal extension
- More aggressive (recurrence, distant metastasis)

	Johnson et al 1988	Ostrowski et al 1996
Extrathyroidal extension	42% (vs 0%)	82% (vs 3%)
Recurrence	58% (vs 8%)	18% (vs 1%)
Distant metastasis	17% (vs 0%)	---
Mortality	25% (vs 0%)	9% (vs 0%)

* % given in ( ) indicates figures for conventional papillary carcinoma

Immunohistochemical features

A recent study by Ostrowski et al shows the following results for the tall cell variant:

- Frequent (100%) and strong reactivity with LeuM1 (vs 6% for conventional papillary carcinoma)
- Strong and extensive EMA staining

These features have previously been shown to be unfavorable prognostic factors in papillary carcinoma. The authors therefore conclude that these findings corroborate the aggressive behavior of the tall cell variant.

Tall cell variant with extensive lymphocytic infiltration

- A recent study by Ozaki et al (1996) reports 13 examples of the tall cell variant associated with extensive lymphocytic infiltration
- Features correspond to the "Warthin-like tumor" variant previously described by Apel et al (1995)
- None of the 13 patients had recurrence or had died.
- It appears therefore that tall cell variant with a prominent lymphocytic response does not behave aggressively.

Reservations on diagnosing the tall cell variant

- Cells satisfying the criteria for "tall cells" (height more than twice the width) are not uncommon in conventional papillary carcinomas. Thus I believe a tumor should not be considered the tall cell variant unless tall cells are really predominant (>50%).
- It is still not entirely clear whether this variant is of prognostic importance independent of extent of disease or stage. That is, as a group, the tall cell variant is definitely more aggressive than conventional papillary carcinoma. But the behavior of cases that are not large and do not show extrathyroidal extension remains to be defined.
- It is not really a disservice to the patient even if the tall cell feature is missed, since the tumor can usually be recognized to be aggressive by other features, e.g. large size, extrathyroidal extension. There is no good evidence that tall cell papillary carcinomas that do not exhibit extrathyroidal extension requires more aggressive therapy than conventional papillary carcinoma.

Papillary carcinoma: prognostic information

1. Tumor size (good for < 1.5 cm)
2. Stage
   - Extrathyroidal extension worsens the prognosis; completeness of excision should also be assessed.
   - Presence of distant metastasis portends a worse prognosis. (Presence of lymph node metastasis is found not to influence the prognosis according to some studies, but some studies have shown this to worsen the prognosis.)
3. Age (good for age <40 years)
4. Certain histologic variants (as discussed above)
5. Marked cellular atypia (?)
6. Invasion of sizable blood vessels (?)

.....

CASE 2

Salient histologic features

- Prominent papillary pattern
- Also complex tubuloglandular pattern
- Tumor cells are obviously tall columnar
- However, nuclear features do not correspond to those of papillary carcinoma: thus this diagnosis can be excluded
- Rather, the nuclei are markedly pseudostratified and hyperchromatic
- Focally cytoplasm shows clearing or vacuolation

Diagnosis

Thyroid -- **Columnar cell carcinoma** (The above combination of features is characteristic of columnar cell carcinoma)

Columnar cell carcinoma of the thyroid

- An uncommon tumor
- First described by Evans in 1986
- An aggressive form of thyroid carcinoma -- hence the importance of recognition.
- Typically develops widespread metastasis, and mortality occurs within a few years of diagnosis in a high proportion of patients

Different views on the nature of columnar cell carcinoma of thyroid

Some consider it a distinct entity:

- Morphologically different from other thyroid tumor types (and lacking nuclear features of papillary carcinoma)
- Associated with worse prognosis
- Perhaps a form of poorly differentiated thyroid carcinoma?

Some consider it merely a variant of papillary carcinoma ("columnar cell variant of papillary carcinoma")

- May coexist and merge with tall cell papillary carcinoma in some cases, and thus may be biologically a form of papillary carcinoma
- Architectural similarity to papillary carcinoma

Notwithstanding these controversies, the bottom-line is: it should be recognized as a tumor (or papillary carcinoma variant) with a high potential for aggressive behavior.

New controversies on the behavior of columnar cell carcinoma

Study from the AFIP by Wenig et al (published as an abstract)

- Nine cases (7F, 2M)
- Eight cases were encapsulated or showed only limited invasion
- Eight patients were alive and well at 4 months to 4 years; only one died of metastatic disease at 3 years
- Conclusion: Columnar cell carcinoma may not portend an adverse biologic course

Recent study by Evans (1996)

- Four encapsulated cases (3F, 1M)
- All remained well with no metastasis or recurrence
- Conclusion: Encapsulated columnar cell carcinomas, in contrast to invasive ones, have a favorable prognosis

What to make out of the conflicting data?

- Most cases in the AFIP series are probably not genuine columnar cell carcinomas but are papillary carcinomas, since the series shows female predominance rather than male predominance, and since they stated that "nuclear features were those of papillary carcinoma" -- which fundamentally does not fit the definition of columnar cell carcinoma!
- If they are bona fide cases, the prognosis of columnar cell carcinoma (coupled with new data from Evans) appears to depend on the local extent of disease (invasiveness and extrathyroidal extension) -- with those tumors showing encapsulation still associated with a favorable outcome.

A recurrent theme in thyroid tumor pathology is illustrated by Cases 1 and 2:
The "aggressive" histologic types/variants of thyroid tumors are associated with an unfavorable outcome when considered as a group. In the less common circumstances where such tumors are encapsulated or do not show extrathyroidal extension, the prognosis may not be unfavorable at all!

How to tell between columnar cell carcinoma and tall cell papillary carcinoma?

	Columnar cell carcinoma	Tall cell papillary carcinoma
Incidence	Very rare (<1% of thyroid carcinomas)	5%-15% of papillary carcinomas
Sex	M >> F	F >> M
Pattern	Papillary, microglandular, solid	Papillary, follicular
Cytology	Pseudostratified; taller; dark nuclei	Less pseudostratified; paler nuclei; oncocytic cytoplasm

In essence, if a tumor looks like a usual papillary carcinoma (just with somewhat more oxyphilic cytoplasm), it's tall cell papillary carcinoma!
If it gives an impression of endometrioid carcinoma (sometimes even with subnuclear vacuoles or clear cytoplasm) or if it reminds one of colonic carcinoma, it's columnar cell carcinoma!

Another possibly related tumor: FAP-associated thyroid carcinoma

- Familial adenomatous polyposis (FAP)-associated differentiated thyroid carcinoma (Harach et al, 1994):
  - ◊ Can precede development of colonic adenomas
  - ◊ Often multifocal
  - ◊ Cribriform, papillary, trabecular, solid, spindle cell areas
  - ◊ Tall cells with stratification
  - ◊ Nuclei usually hyperchromatic
- Thus there is marked morphologic overlap with columnar cell carcinoma (their relationship remains to be clarified)
- Minor differences from columnar cell carcinoma:
  - ◊ Cells have more cytoplasm
  - ◊ Less marked pseudostratification

CASE 3

Salient histologic features

- Prominent papillary formations
- Nuclear features, however, are not those of papillary carcinoma
- No cellular stratification as characteristic of columnar cell carcinoma
- Prominent blood vessels in the cores
- Granular chromatin and granular cytoplasm
- Focal amyloid deposits

THYROID PAPILLARY LESIONS –
PTC, COLLOID NODULE – A
ADENOMA, OTHERS – INFREQUEN

Immunohistochemistry

- Thyroglobulin -
- Calcitonin +
- Chromogranin +
- CEA +

Diagnosis

Thyroid -- **Medullary carcinoma, papillary (pseudopapillary) variant**

Medullary thyroid carcinoma, papillary variant

- Most are pseudopapillae rather than true papillae (surfaces of "papillae" appear rugged)
- The papillary/pseudopapillary appearance results from poor cellular cohesion, which is a feature commonly observed in medullary carcinoma
- In most cases, more typical features of medullary carcinoma (such as solid growth, packets and amyloid) are found in other areas of the tumor
- One study suggests that this variant has a more favorable prognosis, but evidence is not conclusive since the number of cases studied is small. [I believe that it is probably merely a morphologic variant with no prognostic importance.]
- The greatest importance of its recognition is: *Not to mistaken it for papillary carcinoma!*

How to confirm a diagnosis of medullary thyroid carcinoma?

- Traditionally, histochemistry is the most commonly used technique (Grimelius stain to demonstrate argyrophilia, and amyloid stain).
- Immunohistochemistry has become the gold standard.
- E.M. to demonstrate dense-core granules is rarely required for diagnostic purposes.

For every case, it is preferable to confirm the diagnosis of medullary carcinoma by special studies, because of the implications of the diagnosis!

Immunohistochemical profile of medullary thyroid carcinoma

	Positivity rate
Cytokeratin	100%
Calcitonin	95-100%
Calcitonin-related gene peptide	80-95%
CEA	88-100%
Chromogranin	100%

Recommended immunohistochemical panel for diagnosis of thyroid tumor suspected to be medullary carcinoma

1. *Calcitonin*: Most important, because this is the primary hormone product of medullary carcinoma. Potential pitfall is that some antibodies may be impure, and can give rise to false positive reaction. Weak or faint staining should not be considered sufficient evidence for a firm diagnosis of medullary carcinoma; this can represent false positive or cross-reaction in mitochondria-rich cells.
2. *Chromogranin*: The beauty of chromogranin staining is that it can provide independent confirmation of the neuroendocrine nature of the tumor. Positive staining should increase one's confidence in rendering a diagnosis of medullary carcinoma in the event that calcitonin staining is weak.
3. *Monoclonal CEA* (carcinoembryonic antigen): CEA is positive in the great majority of medullary carcinomas, including the small cell variant (which may be negative or only focally positive for calcitonin and chromogranin). Monoclonal CEA antibody is superior to polyclonal CEA antibody with regards to specificity.

In actual practice, use of both calcitonin and chromogranin antibodies will be sufficient in most situations. For small cell tumors or tumors that look somewhat "odd", it may be helpful to add on CEA antibody to provide additional confirmatory evidence and to exclude paraganglioma.

Take-home messages for Case 3

1. Not all papillary tumors of the thyroid represent papillary carcinomas.
2. Medullary carcinoma can also have a papillary/pseudopapillary pattern.
3. The importance of recognition of medullary carcinoma versus follicular cell neoplasm is related to:
    - Always has malignant potential irrespective of presence or absence of invasion
    - Lack of response to radioactive iodine therapy
    - Hereditary basis in an autosomal dominant pattern in ~20% of cases (see Case 8 for further details)

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Thyroid Tumors with a Follicular Pattern (Cases 4 - 7)

CAUSES OF SOLITARY FOLLICULAR NODULE IN THYROID

- Nodular goiter (colloid/adenomatous nodule)
- Follicular adenoma
- Follicular carcinoma
- Papillary carcinoma, follicular variant
- Poorly differentiated thyroid carcinoma
- Medullary carcinoma, follicular/tubular variant

* The first two account for the great majority of cases!

CASE 4

Salient histologic features

- Circumscribed neoplasm
- Prominent trabeculae (wavy)
- Interspersed vacuoles and abortive follicles
- Nuclear grooves; pseudoinclusions
- Prominent hyaline material merging with the tumor cells

Diagnosis

Thyroid -- **Hyalinizing trabecular adenoma** (also known as "paraganglioma-like adenoma")
[It is a variant of follicular adenoma. The tumor is thyroglobulin-positive, which is particularly strong in the vacuoles and abortive follicles.]

Problems in rendering a diagnosis of hyalinizing trabecular adenoma

- Nuclear features simulate those of papillary carcinoma: they often show nuclear grooves and inclusions; furthermore the calcified colloid material may mimic psammoma bodies. Thus the final diagnosis depends on assessment of overall features.
- Hyalinizing trabecular neoplasms should be assessed no differently from follicular adenoma/carcinoma for vascular/capsular invasion. Tumors with a hyalinizing trabecular appearance should not be automatically considered to be adenomas. Hyalinizing trabecular carcinoma can occur.
- "Hyalinizing trabecular" morphology is a pattern rather than a single tumor type:
    - ◊ Solitary, circumscribed, non-invasive tumor (hyalinizing trabecular adenoma)
    - ◊ Solitary tumor with invasion (hyalinizing trabecular carcinoma)
    - ◊ Focal phenomenon in other lesions, e.g. papillary carcinoma, FAP-associated thyroid carcinoma, multinodular goiter, and even thyroiditis.

- A diagnosis of hyalinizing trabecular adenoma should be confirmed by immunohistochemistry, because there are tumors that can closely mimic its appearance:
    - ◊ Medullary carcinoma
    - ◊ Paraganglioma
- Another potentially confusing issue is that hyalinizing trabecular adenoma may occasionally show focal staining for chromogranin -- but of course they are positive for thyroglobulin, which should be negative in medullary carcinoma and paraganglioma.

How does hyalinizing trabecular adenoma differ from a follicular adenoma with trabecular pattern (trabecular adenoma)?

- Trabeculae are wavy rather than straight
- Prominent hyaline material
- Nuclear features overlapping with those of papillary carcinoma (thus often mistaken for papillary carcinoma on fine needle aspiration cytology)

Controversies on the exact nature of hyalinizing trabecular adenoma

It has been postulated by some authors that it may represent an unusual variant of papillary carcinoma:

- Nuclear features simulate those of papillary carcinoma
- Some cases are associated with definite papillary carcinoma in the same gland

Notwithstanding these controversies, hyalinizing trabecular neoplasms that are totally encapsulated should still be called "hyalinizing trabecular adenoma" because all such tumors as reported in the literature have behaved in a benign fashion. The behavior of those tumors showing capsular or vascular invasion, i.e. hyalinizing trabecular carcinoma, is less certain because few cases have been reported so far.

CASE 5

Salient histologic features

- Solitary encapsulated tumor
- Thick fibrous capsule
- Small follicles (some lined by Hurthle cells)
- Lacking cytologic features of papillary carcinoma
- Capsular invasion (total penetration through fibrous capsule; in some slides, this feature is not seen and there is only a satellite tumor nodule located immediately beyond the thick fibrous capsule)

Diagnosis

Thyroid -- **Follicular carcinoma (with focal Hurthle cell features), minimally invasive type**

How to assess solitary follicular lesion of the thyroid?

1. The first step is to assess the cytology. If features of papillary carcinoma are present, the diagnosis is "papillary carcinoma, follicular variant". In such circumstance, it is immaterial whether or not there is invasion.
2. If features of papillary carcinoma are lacking, assess the architecture and also compare with the follicles in the surrounding thyroid.
3. If the lesion is of low cellularity, with large follicles, papillary hyperplasia and similar cytoarchitectural features to adjacent thyroid, the most likely diagnosis is "nodular goiter".
4. For a cellular follicular nodule distinct from the adjacent thyroid tissue, the diagnosis is that of a follicular neoplasm. The distinction of follicular carcinoma from follicular adenoma rests purely on the identification of capsular or vascular invasion in the former.

Colloid nodule (nodular goiter) or follicular adenoma?

- Some cases are very easy to distinguish.
- But some cases can be very difficult to distinguish: the dividing line between cellular colloid nodule and follicular adenoma is somewhat arbitrary.
- The distinction is not very important for management purposes as long as there is no vascular or capsular invasion. That is, if uncertain, the lesion should be assessed as for follicular neoplasm.
- Defined in the commonly accepted sense (non-encapsulated; not uncommonly multiple; follicles similar to those in the surrounding; some large follicles), colloid (adenomatous) nodules have been usually shown to be polyclonal lesions on molecular analysis, while follicular adenomas are usually shown to be monoclonal lesions.

Follicular adenoma or follicular carcinoma?

- The *only criteria for distinction of follicular carcinoma from follicular adenoma are:*
  - ◊ *Vascular invasion or*
  - ◊ *Capsular invasion.*
- Cellular atypia per se does not count. Tumors showing significant cellular atypia but no invasion are simply designated "atypical adenoma".
- Strict criteria must be applied for the diagnosis of follicular carcinoma, i.e. capsular or vascular invasion must be convincing.

Why should we apply strict criteria in diagnosing follicular carcinoma?

- Minimally invasive follicular carcinoma (the form that will cause problem in recognition of capsular or vascular invasion) has an excellent prognosis; the long term cumulative death rate is only ~3%.
- The metastatic rate for tumors showing vascular invasion is ~5%.
- The metastatic rate for tumors showing capsular invasion only is ~1%.
- Thus lobectomy already represents an adequate treatment for these tumors.
- A conservative approach is therefore justified.

Assessment of vascular invasion

Criteria

- The tumor plug should lie in vascular spaces that occur within or outside the fibrous capsule; vascular spaces within the tumor proper are not acceptable for purposes of assessment of vascular invasion.
- The tumor cluster should be covered by endothelium. The only situation when this requirement can be waived is when smooth-contoured tumor thrombus is seen attached to vascular wall (presumably this may be a recent event and full endothelialization has not yet taken place).
- The need to demonstrate attachment to vessel wall is controversial. Personally I consider this to be unnecessary. The point of attachment is so focal that it can be difficult if not impossible to demonstrate in some cases.

Features that do not count for vascular invasion

- Irregular, non-endothelialized tumor cluster floating in vascular space (merely representing artefactual detachment at surgery or during specimen handling).
- Tumor bulging against blood vessels in the tumor proper (this is because the high vascularity does not permit proper evaluation of vascular invasion).
- Tumor nest slightly bulging against blood vessels within the fibrous capsule (this is because it is difficult to tell in such situation whether the tumor nest is within the vascular space or in the fibrous stroma).
- Lack of endothelial lining in the space (indicative of mere retraction artifact).

Can ancillary tests help to highlight or confirm vascular invasion?

- Elastic stain is only rarely useful, because the involved blood vessels are almost always thin-walled.
- Immunostaining for endothelial markers is only very occasionally helpful, but results can be erratic, i.e. even obvious endothelial cells may not stain up.
    - ◊ CD31, coupled with wet heat antigen retrieval, is probably the best.
    - ◊ Ulex europaeus labeling results are often erratic.
    - ◊ CD34 suffers the drawback that some stromal cells can also stain up, complicating interpretation.
    - ◊ Factor VIII-related antigen is not sensitive enough.

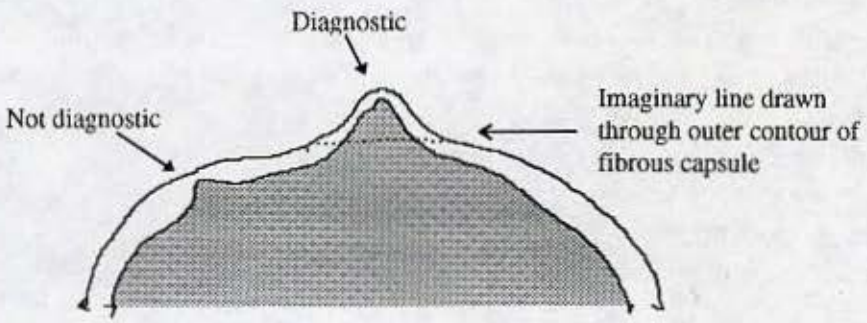
Assessment of capsular invasion

Criteria

- Buds should push completely through the fibrous capsule.
- Mushroom-shaped buds are always significant (indicating active invasion).
- On the occasion of a small nodule located immediately outside an intact capsule, it should show similar cytoarchitectural features as the main tumor for it to be considered evidence of capsular invasion (just that the exact point of transgression cannot be demonstrated). This is to distinguish from an incidental small colloid nodule or adenoma that happens to occur adjacent to another adenoma.

Special features to note in assessment of capsular invasion

- If there are neoplastic follicles oriented perpendicularly within the capsule, this is indicative of an active invasive process. This finding is therefore always significant, and should lead to examination of multiple levels and further blocks for more definite evidence of total transgression of the fibrous capsule.
- Similarly, mushroom-shaped buds are highly significant, suggesting active invasion into the capsule.
- On the other hand, follicles oriented in a parallel fashion within the fibrous capsule are less significant, because this may merely represent passive entrapment in the process of capsular sclerosis.
- Total transgression of the capsule is considered to have occurred if the tumor bud extends beyond the imaginary line drawn through the outer contour of the fibrous capsule. The invasive bud may still be clothed by a thin fibrous capsule (probably new capsule deposited external to the invasive bud).



Features which do not count for capsular invasion

- Irregularities of contour along inner border of fibrous capsule, with no breaching of the external border or external contour of the fibrous capsule.
- Isolated follicles or cells within the fibrous capsule (esp. for those aligned parallel to the capsule). In such circumstance, one cannot tell between active invasion and passive entrapment.
- Fine-needle aspiration-associated capsular rupture, which can be recognized by the following features:
  - ◊ "Invasive" bud is often in continuity with a needle tract or hemorrhagic patch in the parenchyma
  - ◊ Tumor bud in fibrous capsule is typically associated with blood, hemosiderin and some inflammatory cells
  - ◊ The buds are always small and do not have a mushroom contour
  - ◊ The cells in the invasive bud often appear degenerated
  - ◊ Such buds are at most found in one or two foci

Features warranting more careful search for invasion in a follicular neoplasm

1. Thick fibrous capsule (it has been postulated that the sclerosis may represent a reaction to the invasive process)
2. High cellularity, i.e. tumors that are predominantly solid, trabecular or microfollicular
3. Diffuse nuclear atypia
4. Readily identifiable mitotic figures
5. Hurthle cell neoplasms (among which 10-30% are malignant, a figure higher than for non-Hurthle cell follicular neoplasms)
6. Presence of perpendicularly aligned follicles in the fibrous capsule, or mushroom-shaped tumor bud

These features, per se, are not diagnostic of follicular carcinoma. Capsular or vascular invasion has to be found for such a diagnosis to be made.

Can newer techniques help in distinction between follicular carcinoma and follicular adenoma?

- Unfortunately, no.
- Immunohistochemical markers, morphometry, ploidy analysis and oncogene markers have so far failed to provide reliable help in this respect.
- The current gold standard in diagnosis is still morphologic assessment.

Subtypes of follicular carcinoma

	Minimally invasive (encapsulated)	Widely invasive (frankly invasive)*
Pathology	Totally encapsulated with no gross invasion; invasion identified on histologic examination	Obvious invasion of adjacent thyroid tissue grossly; may also include cases with invasion of >4 blood vessels
Local recurrence	Rare	Yes
Metastasis	Metastasis rare (bone, lung), and often late	Distant metastasis in 30-60% (lung, bone, brain, liver)
Long term mortality	Low (3-5%)	Fairly high (~50%)
Treatment	Curable by lobectomy or subtotal thyroidectomy	Total thyroidectomy and radioactive iodine

* It overlaps greatly with "poorly differentiated thyroid carcinoma".

The nature of Hurthle cell neoplasm

Hurthle cell neoplasm is best considered a variant of follicular neoplasm, and assessed no differently regarding malignancy. Some distinctive features of Hurthle cell neoplasm are:

- Brown color
- Often with prominent nucleoli
- May simulate papillary carcinoma due to presence of some papillae and calcified colloid
- Higher chance of infarction following fine needle aspiration
- Takes up radioactive iodine less satisfactorily
- More likely to be malignant, and perhaps also more aggressive than non-Hurthle follicular carcinoma
- More likely to show lymph node metastasis

Why bother to distinguish between follicular carcinoma and papillary carcinoma?

Follicular carcinoma	Papillary carcinoma
Usually unifocal	Usually multifocal
Predominantly blood-borne spread	Predominantly lymphatic spread (lymph node metastasis in ~50% of cases)
Diagnosis based on identification of invasion	Diagnosis based on cytologic features
ras mutation in >50%, usually 61 Glu-->Arg	ras mutation in 17%; ret protooncogene involved in some cases

Benign conditions that may mimic follicular carcinoma

- Dyshormonogenetic goiter
- Adenomatous (cellular) nodule of multinodular goiter
- Regenerated thyroid after thyroidectomy (often in the form of multiple nodules, some of which may occur among skeletal muscle)
- Cellular/atypical follicular adenoma
- Follicular adenoma with fine needle aspiration-associated changes (capsular rupture or reactive atypia around needle tract)

CASE 6

Salient histologic features

- Solitary encapsulated tumor
- Purely follicular
- Some follicles are elongated or irregular shaped
- Follicles lined by cells with clear nuclei that are "up and down"

Diagnosis

Thyroid -- **Papillary carcinoma, encapsulated follicular variant**

Papillary carcinoma: follicular variant (This variant behaves no differently from conventional papillary carcinoma)

Diagnosis of those showing frank invasion usually poses no problem

- Often accompanied by sclerosis
- Nuclear features of neoplastic follicles are abruptly different from those of the adjacent/invaded thyroid follicles

Diagnosis of encapsulated variant of papillary carcinoma is very difficult

- Even more difficult for the macrofollicular variant (which may mimic nodular goiter)
- Strict criteria must be applied for diagnosis

The scenario of a solitary encapsulated follicular lesion of the thyroid with some clear nuclei

The problems

This is in fact one of the commonest problems in thyroid pathology. This is a real problem, because papillary carcinoma do not always exhibit all the typical nuclear features known for this neoplasm. On the other hand, follicular adenoma (or even nodular goiter) can have clear or even grooved nuclei, albeit focal in nature.

The major differential diagnoses in such a circumstance are:

(1) Papillary carcinoma, encapsulated follicular variant

(2) Follicular adenoma

The clinical implications of the diagnoses

Papillary carcinoma, encapsulated follicular variant	Follicular adenoma (with clear nuclei)
Excellent prognosis ~100% survival No recurrence or further metastasis after treatment	Totally benign lesion

The strategy

- Since encapsulated papillary carcinoma is of such excellent prognosis, there is no harm underdiagnosing it.
- A patient given such a diagnosis will carry with him/her all his/her life the stigmata of malignancy.
- Thus, *if uncertain, always err on the benign side!*
- A diagnosis of encapsulated follicular variant of papillary carcinoma should be made only in the presence of overwhelmingly convincing histologic features, i.e. typical nuclear features and typical supporting features. No single histologic criterion is pathognomonic: a constellation of features has to be considered.

What constitute convincing nuclear features of papillary carcinoma?

- Crowded, overlapping nuclei (manifesting as "up and down" nuclei with no polarity).
- Pale chromatin, which may be up to ground-glass appearance.
- Preferably frequent nuclear grooves.
- Presence of at least one or two nuclear pseudoinclusions.
- Oval-shaped rather than round nuclei.

* At least a few of these features need to be present throughout the tumor.

What constitute convincing supportive findings for diagnosis of papillary carcinoma?

- Elongated, tubular or irregular-shaped follicles rather than round follicles.
- Dark-staining colloid, which contrasts with the pale-staining nuclei.
- Abortive papillae projecting into follicles.
- Psammoma bodies (which are practically pathognomonic), although calcified colloid (common in hyalinizing trabecular adenoma and Hurthle cell neoplasms) may sometimes be mistaken for psammoma bodies.
- Presence of multinucleated giant cells (histiocytes) in the lumens of follicles [personal observation].

Pseudoclear nuclei mimicking those of papillary carcinoma

- Pseudoclear nuclei can sometimes be seen in follicular adenoma or adenomatoid nodule: this "blowing up" or "clearing" of the nuclei is probably related to delayed fixation. Such nuclei are most common in the central portion of the tumor, where the fixative reaches it at the latest time. Therefore disregard clear nuclei confined to the central zone of the tumor.
- Bubbly nuclei may result from suboptimal fixation/processing of the tissue: they differ from pseudoinclusions by the coagulated appearance and lack of discrete chromatin granules. Usually many nuclei are affected in certain regions of the tumor: a most uncommon phenomenon for nuclear pseudoinclusions.

What to do for an encapsulated follicular lesion with some but not all features of papillary carcinoma?

There are several options:

1. Simply call it "follicular adenoma" (the preferred option, i.e. "doing no harm").
2. If worried, may call it "atypical adenoma" or "follicular adenoma with clear nuclei".
3. May also consider the uncommon possibility of papillary carcinoma arising in a follicular adenoma (but features of papillary carcinoma have to be convincing in some foci).

Will special studies help in diagnosis of papillary carcinoma in such equivocal situations?

Unfortunately, no.

A variety of antibodies have been tried, but none shows high sensitivity and high specificity for rendering a diagnosis of papillary carcinoma. Some examples are:

- High molecular weight cytokeratin, such as 34βE12; the problem is that even for typical papillary carcinoma, the staining is focal or patchy.
- HBME-1, a newly available mesothelial marker: it is alleged to stain thyroid carcinomas but only rarely benign thyroid tumors. This finding requires further studies for verification.
- S-100 protein
- Epithelial membrane antigen

When to suspect that a "follicular adenoma" may represent papillary carcinoma (follicular variant)?

- Many elongated or irregular-shaped follicles
- Dark-staining colloid
- Abortive papillae in some follicles
- Any psammoma body
- Many clear nuclei

CASE 7

Salient histologic findings

- Widely invasive tumor
- Sclerotic stroma
- Solid and microfollicular, with focal papillae
- Festooning pattern
- High N/C ratio; dark round nuclei
- Necrosis
- Vascular invasion (seen only in some slides)

Immunohistochemistry

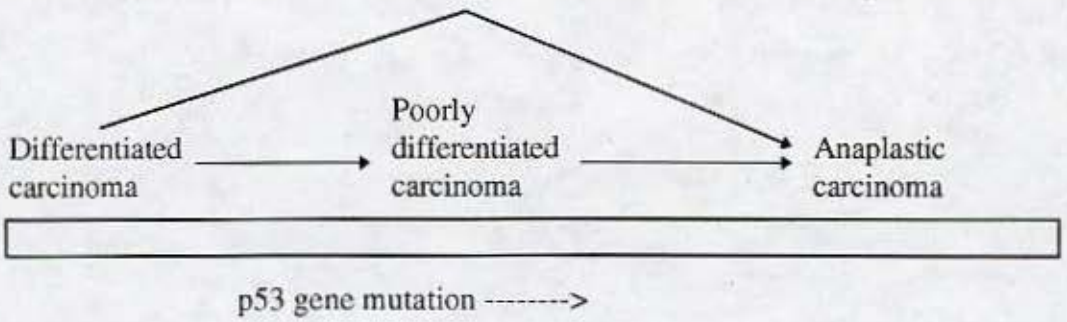
- Thyroglobulin + (especially in the microfollicles)
- Calcitonin -
- Chromogranin -

Diagnosis

Thyroid -- **Poorly differentiated (insular) carcinoma**

What is poorly differentiated thyroid carcinoma?

- Thyroid tumors showing histologic and biologic features intermediate between the differentiated carcinomas and anaplastic carcinomas.
- Some are related to follicular carcinoma and some are related to papillary carcinoma, but use of the category "poorly differentiated thyroid carcinoma" removes the need to specify the exact relationship with follicular carcinoma or papillary carcinoma.
- Commonest type of poorly differentiated thyroid carcinoma is insular carcinoma; another term proposed is "primordial cell carcinoma".
- Other growth patterns and cytology possible, e.g. medium-sized or large cells, predominance of solid or trabecular pattern.
- Different investigators have adopted different criteria for inclusion in their studies.
- Differentiated thyroid carcinoma may transform to poorly differentiated carcinoma, and poorly differentiated thyroid carcinoma can transform to anaplastic carcinoma. Occasionally, differentiated thyroid carcinoma may transform directly to anaplastic carcinoma. Mutations in the tumor suppressor gene p53 may mediate the transformation towards anaplastic carcinoma.



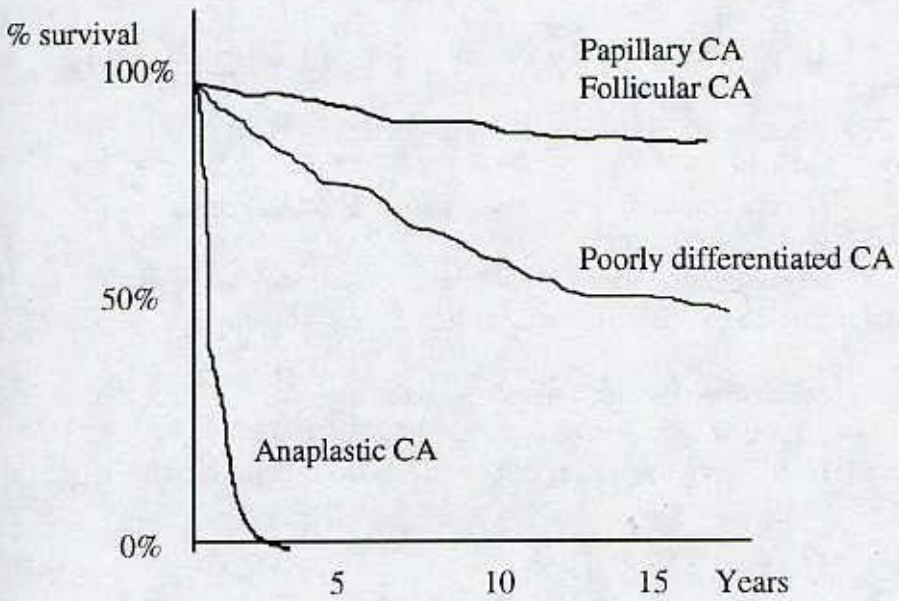
Poorly differentiated thyroid carcinoma

Clinical features

- Usually affects middle-aged or old-aged subjects
- Mean age 55.7 years (approximately 10 years older than for the differentiated thyroid carcinomas).
- Female > Male
- Presenting with thyroid mass
- High frequency of nodal or distant metastasis, which occurs in ~50% of cases.

Behavior

- Locally invasive
- Local recurrence after surgery
- Tendency to metastasize to lymph node, lung and bone
- Follow-up:
  - ◊ Died of disease 28%
  - ◊ Alive with disease 31%
  - ◊ Alive and well 41%
- It is likely that at least a proportion of those alive with disease will eventually die. The projected long-term mortality therefore approaches 50%.



Poorly differentiated thyroid carcinoma: importance of recognition

- Much more aggressive than usual follicular/papillary carcinoma.
- Many cases reported as "widely invasive follicular carcinoma" actually represent poorly differentiated thyroid carcinoma.

Poorly differentiated (insular) carcinoma seen as a focal phenomenon in otherwise typical papillary or follicular carcinoma: what are the clinical implications?

- Focal insular carcinoma confined to non-invasive portion of minimally invasive follicular carcinoma: probably does not worsen prognosis.
- Focal insular carcinoma found in invasive areas: implication unclear, but may potentially slightly worsens prognosis. Such cases can be designated "papillary/follicular carcinoma with focal insular carcinoma".

Poorly differentiated thyroid carcinoma: major mimickers and vice versa

- Medullary carcinoma: The packeting pattern and microfollicular pattern can be seen in both medullary carcinoma and poorly differentiated thyroid carcinoma; the amyloid of medullary carcinoma may mimic the sclerotic stroma commonly seen in poorly differentiated thyroid carcinoma. Immunohistochemical studies are most helpful for the distinction.
- Solid variant of papillary carcinoma (but nuclear features are those typical of papillary carcinoma)
- Anaplastic carcinoma, "small cell type"

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Solid Tumors of the Thyroid (Cases 8 - 9)

SOLID TUMORS OF THE THYROID

Causes

- Papillary carcinoma, solid variant
- Follicular neoplasm, solid/cellular variant
- Medullary carcinoma
- Anaplastic carcinoma
- Malignant lymphoma

Approach to diagnosis

- Careful evaluation of cytologic features
- Assessment of architectural pattern [Remember that medullary carcinomas are not uncommonly circumscribed or encapsulated!]
- Perform immunohistochemical stains as required.

CASE 8

Salient histologic findings

- Solid growth and packets
- Prominent delicate fibrovascular septa
- Focal loss of cellular cohesion ("dehiscence")
- Focal amyloid deposits
- Finely granular chromatin
- Focal large pleomorphic nuclei
- Granular cytoplasm

Immunohistochemistry

- Cytokeratin +
- Thyroglobulin -
- Calcitonin +
- CEA +
- Chromogranin +

Diagnosis

Thyroid -- **Medullary carcinoma, classical type**

Medullary thyroid carcinoma: behavior

- Lymph node metastasis common (1/3 to 2/3 of cases)
- Local recurrence after surgery
- Distant metastasis (can be delayed), e.g. liver, bone, lung, adrenal. But presence of distant metastasis can sometimes still be compatible with long-survivals.
- Survival rate: 5 years = 80%; 10 years =67%

Clues for diagnosis of medullary thyroid carcinoma

- Amyloid, although its presence is not a prerequisite for diagnosis.
- An endocrine/neuroendocrine-look, i.e. delicate fibrovascular septa, finely stippled chromatin and granular cytoplasm. The *delicate fibrovascular septa* that traverse the tumor constitute a most important to clue to recognition of medullary carcinoma versus other thyroid tumors.
- Cellular dehiscence, a very common feature observed in medullary carcinoma.

Practice points

- A diagnosis of medullary carcinoma should always be confirmed by immunohistochemistry.
- All relevant prognostic information should be provided.
- Should identify the hereditary form of medullary carcinoma (accounting for 20% of all cases)

Tumors which may mimic medullary carcinoma, and vice versa

- Poorly differentiated thyroid carcinoma
- Hyalinizing trabecular adenoma (due to the focal packeting pattern and hyaline material mimicking amyloid)
- Paraganglioma (due to the packeting and prominent fibrovascular stroma)
  - ◊ This possibility should be considered when a tumor suspected to represent "medullary carcinoma" is negative for calcitonin and CEA
  - ◊ In such circumstance, cytokeratin immunostaining is most helpful (negative in paraganglioma, but positive in medullary carcinoma).
  - ◊ S100 protein positive sustentacular cells can also be demonstrated in paraganglioma.

Prognostic factors of medullary thyroid carcinoma

- Size of tumor: small tumors have a much better prognosis and are potentially curable; that is why it is important not to miss the hereditary form of the tumor, so that affected members of the family can be subjected to thyroidectomy as early as possible (when tumor is still small).
- Lymph node metastasis: its presence markedly worsens the prognosis, with 10-year survival rate dropping from 86% (node negative) to 46% (node positive).
- Aggressive variants:
  - ◊ Small cell type
  - ◊ Giant cell type (questionable)
- High mitotic count or coagulative necrosis: worse prognosis
- Calcitonin-poor tumors are more aggressive than those in which the tumor cells show diffuse strong immunoreactivity for calcitonin
- Hereditary form: familial medullary thyroid carcinoma and MEN2a tumors are relatively indolent, while those of MEN2b are aggressive.

The hereditary form of medullary thyroid carcinoma (MTC)

There are three different forms of hereditary medullary carcinoma, all showing autosomal dominant inheritance.

Familial MTC only	MEN2a	MEN2b
MTC	MTC Pheochromocytoma Parathyroid hyperplasia +/-	MTC Pheochromocytoma Mucosal neuroma Marfanoid habitus

Features characteristic of the hereditary form of medullary carcinoma

- Younger age of onset
- More likely to be multifocal
- More likely to be bilateral
- Arising in a background of C-cell hyperplasia

Why is it important to recognize the hereditary form of medullary carcinoma?

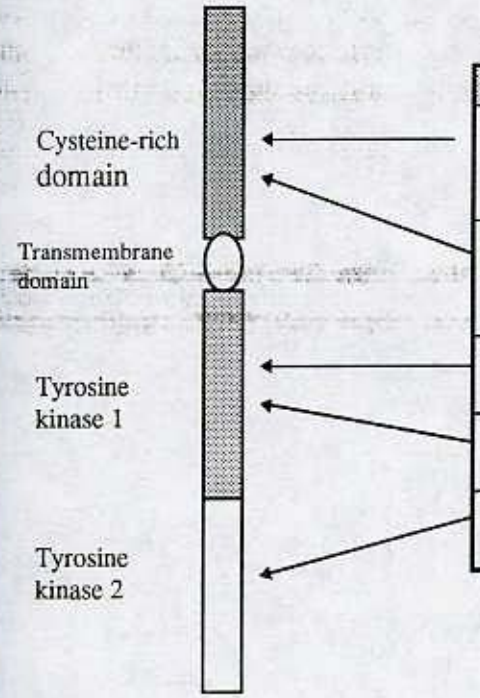
- The family members have to screened to see who are carriers of the disease (mutated gene).
- Affected members should be closely followed up and given early treatment:
  - Small, incidentally found medullary carcinomas are more curable than larger tumors.
  - Pheochromocytoma can potentially be fatal due to hypertensive crisis.

Traditional approach for identifying the hereditary form of medullary carcinoma: By looking for C-cell hyperplasia (its presence being indicative of the hereditary form)

- The traditional approach is to look for C-cell hyperplasia in the uninvolved portions of the thyroid gland of the patient with medullary carcinoma. C-cell hyperplasia appears to be the basic and initial process in patients with hereditary predisposition to medullary carcinoma, and this forms the soil upon which further genetic changes occur, allowing medullary carcinoma to emerge.
- However, there are many pitfalls in this approach, and there are no good criteria for diagnosing C-cell hyperplasia.
- The *diffuse form* is very difficult to recognize in routine histologic sections, and requires assessment of sections immunostained for calcitonin or neuroendocrine markers. It has no universally agreed diagnostic criteria, e.g. >10 C-cells per low power field, >50 C-cells per low power field.
- The *nodular form of C-cell hyperplasia* is defined as "complete obliteration of follicular space by C-cells with formation of solid intrafollicular aggregates". It can thus be recognized on routine histologic sections (and can be further confirmed by immunohistochemistry). The problem is that distinction from early medullary carcinoma or intrathyroid spread of medullary carcinoma is difficult.
- To complicate matters, many other conditions can show C-cell hyperplasia (usually of the diffuse form), e.g. around any thyroid neoplasm (such as follicular adenoma, follicular carcinoma, papillary carcinoma), Hashimoto's thyroiditis, old age.

The most reliable current approach for identifying the hereditary form of medullary carcinoma: molecular analysis

- The most reliable way to identify the hereditary form of medullary carcinoma (familial MTC, MEN2a or MEN2b) is molecular analysis.
- Germline mutation in the *RET* protooncogene can be identified in practically all cases. Germline mutation means that the mutation is found in *all* cells in the body and is thus heritable (usually inherited from a parent, although it can rarely represent a new mutation in the index case).
- The patterns of *RET* gene mutation are different for the different forms of hereditary medullary carcinoma.
- Detection of germline mutation in the *RET* gene reliably identifies a person as belonging to the hereditary form of medullary carcinoma. This is important, because the family history may sometimes by non-revealing or non-contributory. If the index is found to show germline mutation, the family members should similarly be screened.
- To detect germline mutations, the following specimens can be used for analysis: peripheral blood (extracting DNA from circulating leukocytes) or paraffin-embedded non-tumorous tissues (such as uninvolved thyroid gland or lymph node).



Exon	*Codon*	*Syndrome*
10	609, 611, 618, 620	MEN2a Familial MTC
11	634	MEN2a Familial MTC
13	768	Familial MTC
14	804	Familial MTC
16	918	MEN2b

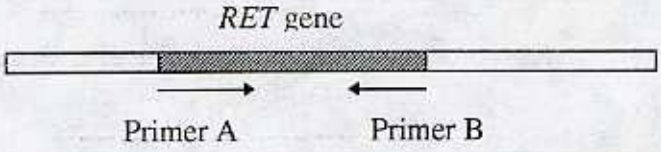
- There is correlation between the site of mutation in the *RET* gene and clinical manifestations.
- Involvement of codon 634 of exon 11 (occurring in ~80% of MEN2a), such as change of cysteine residue to tyrosine, arginine or phenylalanine, is highly predictive of development of pheochromocytoma.
- Involvement of codon 634 of exon in the form of Cys(TGC)-->Arg(CGC) is predictive of development of parathyroid disease.

RET protooncogene

What is the *RET* protooncogene?

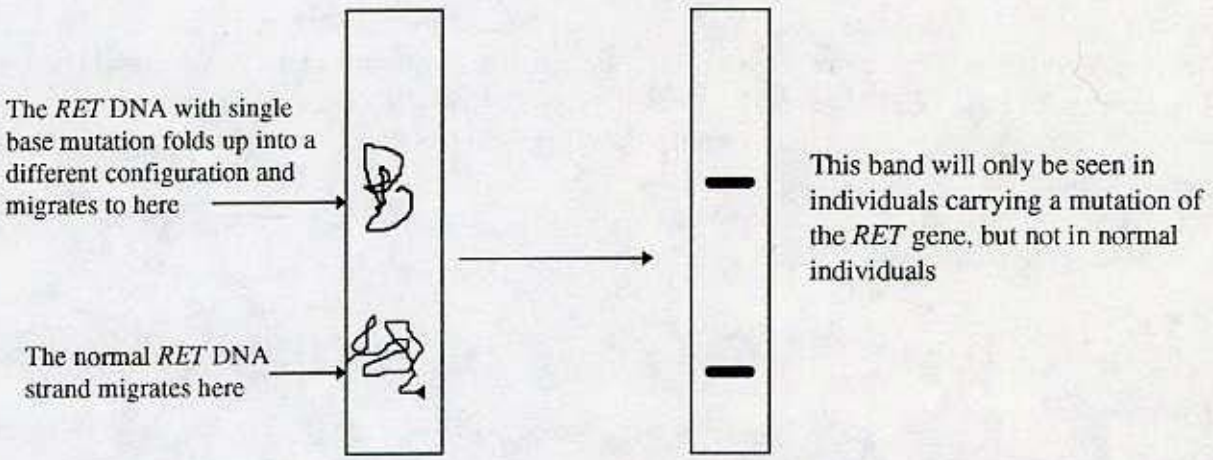
- *RET* has at least 20 exons (size >60 kb).
- The gene is located on chromosome 10q11.
- The gene codes for transmembrane receptor tyrosine kinase (1072 or 1114 amino acids).
- *RET* is normally widely expressed in neuroendocrine tissues (such as C cells, adrenal medulla, parathyroid) and nerves, regulating tissue growth and differentiation.
- *RET* is a protooncogene; this is the only known hereditary cancer syndrome in which a protooncogene is involved -- all other known syndromes have implicated a tumor suppressor gene rather than protooncogene.
- The somatic missense mutation of *RET* in hereditary medullary carcinoma results in gain of function (forming active dimers with increased stability in MEN2a, and altered substrate specificity in MEN2b), leading to increased proliferative activity of endocrine/neuroendocrine cells in the body.

How to detect presence of mutation in *RET* gene?



POLYMERASE CHAIN REACTION (PCR)

ANALYSIS BY SINGLE STRAND CONFORMATIONAL POLYMORPHISM (SSCP): Electrophoretic separation of amplified DNA by the conformation of the single-stranded DNA, not by size as in the usual electrophoresis



Appearance of the gel after electrophoresis (SSCP)

Somatic mutations in the *RET* protooncogene

- In contrast to germline mutation (which is present in every cell in the body), somatic mutation is found only in some cells (usually tumor).
- Somatic mutations cannot be passed on to the next generation.
- In sporadic medullary thyroid carcinoma, somatic mutations of *RET* are detected in 14%-67% of cases (involving mostly exon 16, sometimes exon 13); such cases do not show germline mutation of the *RET* gene.

- In sporadic pheochromocytoma, somatic mutations of *RET* are very uncommon (0-15% of cases).
- In sporadic parathyroid hyperplasia or neoplasm, no somatic mutations of *RET* gene have been found.
- These findings indicate that the *RET* protooncogene does not contribute to the development of sporadic pheochromocytoma and parathyroid hyperplasia/neoplasia.

Other conditions in which the *RET* gene is involved

(1) Papillary thyroid carcinoma

- *RET* gene is implicated in a proportion of papillary carcinomas (2.5% in Saudi Arabia, 6% in Japan, 35% in Italy, 2/3 of Chernobyl-related cases).
- The *RET* gene is juxtaposed with an activating gene partner, such as *PTC1, PTC2* or *PTC3*, resulting in aberrant activation of *RET* gene in thyroid follicular epithelium.
- The mechanism is by intrachromosomal inversion or by translocation t(10;17).

(2) Hirschsprung's disease

- In approximately half of the cases, the *RET* gene is involved.
- The mutations are widely distributed over the many exons of this gene.
- In contrast to hereditary medullary carcinoma, the mutation results in loss of function (substitution, deletion, premature stop codons).

CASE 9

Salient histologic findings

- Solid growth (sheets, islands)
- Polygonal cells, plump spindly cells, and delicate spindly cells
- Significant cellular atypia and mitotically active
- Squamous areas
- Sclerotic areas
- Obliteration of blood vessels
- In focal areas, portions of a Hurthle cell neoplasm are identified, merging gradually with the squamous cell carcinoma or undifferentiated carcinoma (not seen in some slides)

This is obviously a high grade carcinoma. The problem is whether to call it an anaplastic carcinoma or squamous cell carcinoma.

Immunohistochemistry

- Cytokeratin + (including a proportion of the spindly cells)
- Thyroglobulin - (positive in the Hurthle cell tumor portion; there is weak staining in the pleomorphic tumor cells that are in the immediate vicinity of the Hurthle cell tumor, due to passive uptake)
- Calcitonin -

Diagnosis

Thyroid -- **Anaplastic (squamous cell) carcinoma, arising from a preexisting Hurthle cell neoplasm** [Since the Hurthle cell tumor is "broken up" by the anaplastic carcinoma, proper assessment of capsular or vascular invasion cannot be made. Thus it cannot be ascertained whether it was a Hurthle cell adenoma or Hurthle cell carcinoma.]

Terminology: Anaplastic or squamous cell carcinoma?

- It does not matter.
- For simplicity, it can be called "anaplastic carcinoma" despite presence of definite squamous differentiation, because biologically and clinically these two tumors are no different, and squamous areas often merge into anaplastic areas.
- Both tumors are strongly associated with preexisting differentiated carcinomas (follicular carcinoma or papillary carcinoma, sometimes follicular adenoma). On careful search, this can be found in 50-90% of cases.
- That is, in the thyroid, anaplastic carcinoma and squamous cell carcinoma can be considered to be biologically the same disease entity.

Anaplastic thyroid carcinoma: pathology and behavior

- The morphologic appearances are quite variable, ranging from large polygonal pleomorphic cells to spindly sarcomatoid cells. There can be many interspersed osteoclast-type giant cells.
- Invasion and obliteration of blood vessels is very common.
- Identification of a preexisting differentiated thyroid carcinoma strongly supports a diagnosis of primary carcinoma over metastatic carcinoma.
- Most patients with anaplastic carcinoma die within one year, with a median survival of 4 months. Thus this is a highly aggressive neoplasm.
- The 5-year survival rate is only ~5%.
- Both lymph node and distant metastases are common.

Immunohistochemical profile of anaplastic thyroid carcinoma

- Cytokeratin: positive in only ~50% of cases
- Vimentin: positive in ~50% of cases
- Thyroglobulin: Typically negative (Beware of false positive due to diffusion phenomenon at the interface region with normal thyroid)
- Calcitonin: Negative

Remember that immunohistochemical studies do not contribute much to the diagnosis of anaplastic thyroid carcinoma. A negative cytokeratin reaction does not exclude this diagnosis.

The major differential diagnosis is high grade sarcoma, but it does not matter much in practical terms, because both anaplastic carcinoma and high grade sarcoma are highly aggressive neoplasms. As a general rule, a diagnosis of primary thyroid sarcoma should never be made unless there is extra evidence to substantiate the diagnosis (such as E.M.).

Considerations for squamous cell carcinoma of the thyroid

- Exclude metastasis or invasion from adjacent organs.
- Should not mistake the following low-grade tumors of the thyroid for squamous cell carcinoma:
  - ◊ Papillary carcinoma with squamous foci
  - ◊ Mucoepidermoid carcinoma
  - ◊ Carcinoma with thymus-like element (CASTLE)

Other lesions that may mimic anaplastic carcinoma

- Follicular adenoma/carcinoma with fine needle aspiration-associated reactive atypia
  - ◊ Around needle tract
  - ◊ In response to infarction
- Malignant lymphoma
- Metastatic carcinoma (special stains helpful, e.g. surfactant positivity favors pulmonary origin)
- Sarcomas (very rare)

Does small cell anaplastic carcinoma of the thyroid exist?

- Yes, but extremely rare (small cell neuroendocrine carcinoma).
- Most cases reported in the literature represent:
  - ◊ Malignant lymphoma (majority)
  - ◊ Medullary carcinoma without amyloid
  - ◊ Poorly differentiated thyroid carcinoma
  - ◊ Metastatic small cell carcinoma

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Spindle Cell Lesions of the Thyroid (Cases 10 - 13)

CAUSES OF SPINDLE CELL TUMORS IN THE THYROID

Epithelial

- Medullary carcinoma
- Atypical (follicular) adenoma
- Papillary carcinoma with nodular fasciitis/fibromatosis-like stroma
- SETTLE
- Anaplastic carcinoma

Mesenchymal

- Nerve sheath tumor
- Smooth muscle tumor
- Angiosarcoma
- Solitary fibrous tumor
- Other mesenchymal tumors

Remember that spindly cells are not uncommon in endocrine or neuroendocrine tumors, e.g. medullary thyroid carcinoma, spindle cell carcinoid, endocrine intraductal carcinoma of breast

To arrive at the diagnosis, one needs to assess the overall architecture and cytology. Immunohistochemistry may be required for confirmation of the diagnosis or delineation of direction of differentiation.

CASE 10

Salient histologic findings

- Prominent spindly cells (merging with polygonal cells focally; some polygonal cells are vacuolated and contain mucin)
- Spindly cells in fascicles
- Prominent delicate fibrovascular septa
- Stippled chromatin; granular cytoplasm
- Focal amyloid globules

Immunohistochemistry

- Cytokeratin +
- Thyroglobulin -
- Calcitonin +
- CEA +
- Chromogranin +
- Synaptophysin +

Diagnosis

Thyroid -- **Medullary carcinoma, spindle cell variant**

(In this case, the prominent delicate fibrovascular septa should provide a strong clue to the correct diagnosis, despite the mesenchymal-like spindle cell growth.)

Problems in diagnosis of medullary thyroid carcinoma

- May not have amyloid deposits
- Many histologic variants that cause problems in recognition
- May even contain mucin (~50%), and thus can be mistaken for conventional adenocarcinoma, especially in a metastatic site such as lymph node
- Remember that a cervical lymph node harboring a calcitonin-positive metastatic carcinoma is not invariably caused by medullary thyroid carcinoma. Laryngeal carcinoid tumors also commonly produce calcitonin.

Variants of medullary thyroid carcinoma

1. Classical (exemplified by Case 8)
2. Papillary (exemplified by Case 3)
3. Spindle cell (exemplified by this case)
4. Glandular/follicular/tubular
5. Clear cell
6. Oncocytic
7. Squamous
8. Pigmented
9. Anaplastic/Giant cell
10. Hyalinizing trabecular adenoma-like
11. Neuroblastoma-like
12. Small cell (may be calcitonin negative, CEA+)

Among these variants, only the small cell type has been convincingly demonstrated to be of prognostic importance (more aggressive behavior).

Fortunately, for these many variants, careful search will often reveal foci that are more typical-looking for medullary carcinoma.

Glandular/follicular variant of medullary carcinoma

- Problematic because it may strongly mimic follicular neoplasm or poorly differentiated thyroid carcinoma.
- The distinction is important because medullary carcinoma is hereditary in ~20% of cases.
- The glandular structures often show concentration of granules along the luminal surface.
- The clues for recognition of this variant as medullary carcinoma are:
  (1) Prominent delicate fibrovascular septa
  (2) Stippled chromatin of the tumor cells

* The diagnosis always requires confirmation by immunohistochemistry.

Oncocytic variant of medullary thyroid carcinoma

- Causes a lot of problem in diagnosis: may be mistaken for Hurthle cell adenoma/carcinoma. This misdiagnosis is potentially consequential, because medullary thyroid carcinoma is hereditary in a proportion of cases.
- Therefore *any "Hurthle cell neoplasm" with prominent fibrovascular septa or funny-looking appearance deserves immunohistochemical evaluation to exclude medullary carcinoma.*

CASE 11

Salient histologic features

- Invasive biphasic neoplasm
- Sclerotic septa, producing nodules/lobules
- Tubulopapillary glands
- Spindly cells in fascicles, with some loose (reticulated) areas
- Spindly cells merging with epithelial elements
- Relatively bland cytology

Immunohistochemistry

- Cytokeratin: Positive in epithelial cells and some spindly cells
- Thyroglobulin: Negative
- Calcitonin: Negative
- CEA: Negative
- Chromogranin: Negative
- S100 protein: Negative
- Actin: Some spindly cells positive

Diagnosis

Thyroid -- **Spindle epithelial tumor with thymus-like element (SETTLE)**

Outcome of patient (Case 11)

Two years after thyroidectomy, the patient had left upper lobectomy because of metastasis in the lung. Subsequently bilateral pulmonary metastases developed, and the patient was given chemotherapy. He died 8 years after presentation. At postmortem, metastatic neoplasm was found in the left pleural surfaces, mediastinal lymph nodes, left main stem bronchus, both lungs, peri-esophageal area, pancreas and kidney.

Differential diagnosis of biphasic neoplasm in the thyroid

1. Anaplastic carcinoma (But not likely for this case in view of the bland cytology)
2. Medullary carcinoma, spindle cell variant (Should be considered, but the lack of neuroendocrine markers and calcitonin do not support this diagnosis)
3. SETTLE (The histology of this case fits this entity very well)
4. Ectopic thymoma (A possibility, but lymphocytes are lacking and the spindly cells are much more delicate and fascicular than in a thymoma)
5. Immature teratoma (No, because organoid tissues are lacking)
6. Other mesenchymal tumors, e.g. synovial sarcoma (Possible, in fact, morphologic distinction between synovial sarcoma and SETTLE is practically impossible except when mucinous glands are seen in the latter. SETTLE generally shows a greater degree of widespread cytokeratin-reactivity in the spindly cells.)

SETTLE of the thyroid

- A tumor believed to be derived from branchial pouch remnants and showing primitive thymic differentiation.
- The spindly cells of this tumor are in fact epithelial (cytokeratin positive, and ultrastructurally showing desmosomes and sometimes tonofilaments).
- Typically occurs in young age (with a mean of 15 years), but older adults are not exempt, as in this case. But in fact this patient has noticed enlarged thyroid for all his life.
- Presenting with a thyroid mass.
- Behavior is somewhat unpredictable, but there is a tendency to develop delayed distant blood-borne metastasis, especially to the lungs and kidneys. This case also illustrates well the characteristic indolent course of the disease, and the typical pattern of metastasis.

Distinction between SETTLE and ectopic thymoma

	SETTLE	***Ectopic thymoma***
Behavior	Malignant (indolent)	Mostly benign
Lobulation	Less well developed	Jigsaw puzzle-like
Spindly cells	More striking and mesenchymal-like	May be present, but less fascicular
Mucinous glands	Seen in some	Extremely rare
Lymphocytes	Few to none	Commonly abundant, and of immature T-cell phenotype

Another thymic-related tumor of the thyroid: Carcinoma with thymus-like element (CASTLE)

- Affects adults
- Tumor located in thyroid gland, most commonly lower pole, and may invade surrounding soft tissues.
- Histology is that of lymphoepithelioma-like carcinoma with a lobulated pattern and pushing margins.
- May show foci of squamous differentiation.
- This is a generally indolent tumor with a propensity to metastasize to cervical lymph nodes (about half of cases). Can recur, often after long intervals. Distant metastasis is not common.
- One case has been studied for EBV, and is found to be negative.

* *Ectopic hamartomatous thymoma* does not occur in the thyroid, but instead occurs in the soft tissues of the lower neck or supraclavicular region. It is totally benign.

.....

CASE 12

Salient histologic features

- Hypocellular infiltrative lesion
- Dense sclerosis
- Some spindly cells with only mild atypia
- Sprinkling and aggregates of lymphocytes

----> May seriously consider Riedel's thyroiditis

But this case shows features that are most unusual for Riedel's thyroiditis .....

- Many of the "sclerotic" areas represent infarcted tissue, with ghost shadows of blood vessels and total absence of cells
- Definite cytologic atypia identified in focal areas
- Discrete interface with surrounding tissue, suggesting a neoplastic process
- Lymph node involvement
- Vascular invasion by a spindle cell process, not phlebitis as typical of Riedel's thyroiditis

Immunohistochemistry

Cytokeratin +
EMA +
Thyroglobulin -

Diagnosis
Thyroid -- **Anaplastic carcinoma, paucicellular variant**

Paucicellular variant of anaplastic carcinoma
- Uncommon
- Can pose great problems in diagnosis due to low cellularity and subtle cellular atypia. Typically misdiagnosed as Riedel's thyroiditis.
- Prominent vascular invasion ---> Infarction (hence the low cellularity)
- Behaves no differently from conventional anaplastic carcinoma

Riedel's thyroiditis, the major differential diagnosis of paucicellular anaplastic carcinoma
- Very rare in recent literature
- Either a "disappearing" entity or some previously diagnosed cases actually represented paucicellular anaplastic carcinoma
- Occurs in elderly, causing rapid enlargement of a neck mass, with symptoms of compression.
- An inflammatory fibrosclerotic lesion (in the same family as retroperitoneal fibrosis, sclerosing mediastinitis, etc.)
- An infiltrative process, and extrathyroidal extension is common
- Fibrocellular infiltrate
- Destruction of thyroid follicles (no oxyphilic change)
- Chronic inflammatory cells
- Phlebitis
- Prognosis is very good, in contrast to anaplastic carcinoma.
- Major differences from paucicellular anaplastic carcinoma:
    - ◊ Lack of infarcted areas
    - ◊ Lack of cellular atypia
    - ◊ Presence of phlebitis rather than vascular occlusion by spindly cells

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CASE 13

Salient histologic features
- Spindle cell neoplasm
- Bland-looking spindly cells
- Spindly cells intimately associated with abundant collagen
- Richly vascularized (pericytomatous) in areas

Differential diagnosis

- Solitary fibrous tumor (everything compatible, but will require confirmation by CD34 immunostaining)
- Fibromatosis (excluded in view of tumor circumscription and presence of the distinctive alternating cellularity pattern)
- Nerve sheath tumor (possible, and preferably excluded by lack of S100 staining)
- Medullary carcinoma, spindle cell variant (typical features of medullary carcinoma including the delicate fibrovascular septa are not seen in this case)
- Anaplastic carcinoma, spindle cell type (unlikely in this case since there is no cellular atypia)
- Papillary carcinoma with nodular fasciitis/fibromatosis-like stroma
- Spindle epithelial tumor with thymus-like element/SETTLE (not very likely in the absence of a biphasic pattern; furthermore, this case does not display the highly cellular compact spindle cell fascicles commonly seen in SETTLE)

Immunophenotype

- Cytokeratin -
- Vimentin +
- S100 protein -
- Actin -
- Desmin -
- CD34 +

Diagnosis

Thyroid -- **Solitary fibrous tumor**

Solitary fibrous tumor: other terms

- Solitary fibrous mesothelioma
- Localized mesothelioma
- Submesothelial fibroma

These are misnomers, because the neoplastic cells are not mesothelial cells or their derivatives, and the tumor can occur in sites totally unrelated to serosal cavities.

Solitary fibrous tumor: Original recognized sites of occurrence

- Pleura
- Peritoneal cavity (including liver capsule, omentum, retroperitoneum, etc.)
- Pericardium
- Mediastinum
- Pulmonary and hepatic parenchyma

Solitary fibrous tumor: Newly recognized sites of occurrence

It has now been reported in practically every conceivable site of the body.

- Upper respiratory tract
- Orbit
- Thyroid
- Soft tissue
- Salivary gland
- Kidney
- Meninges
- Breast
- Spermatic cord

(Although it has not been specifically described to occur in the adrenal gland and parathyroid gland, this tumor can potentially occur in these sites.)

Solitary fibrous tumor of the thyroid

- Very rare
- Only three cases have been reported in literature.
- Two women, 1 man
- All patients have been adults, and they remained well at 4 to 5 years.

Solitary fibrous tumor: clinical features and behavior

- Now a "fashionable" diagnosis
- Mass lesion or asymptomatic
- Rare cases may be associated with hypoglycemia
- Outcome:
  - ◊ Mostly benign
  - ◊ Recurrence may sometimes occur
  - ◊ Metastasis very rare
- In the pleural examples, all those with a pedunculated growth pattern behave in a benign fashion irrespective of histologic features (including cellular atypia). Those that are infiltrative, especially those with high cellularity, atypia and mitoses are more likely to behave in a malignant fashion.
- Solitary fibrous tumors occurring outside serosal cavities have all pursued a benign course (rare recurrence and no metastasis): this may not be due to differences in biologic features, but due to the relatively new recognition of this tumor in such sites (when only the more typical examples are recognized as such, and with those showing atypia being diagnosed as something else).

Solitary fibrous tumor: histologic features

- Well circumscribed
- Normal tissues may be entrapped in the periphery
- Typically showing alternating cellular and hypocellular areas
- Patternless growth of short spindly or stellate cells with scanty cytoplasm (the "pink" appearance appreciated at medium magnification is merely due to the intercellular collagen fibrils)
- Nuclear atypia absent or only mild
- Abundant collagen throughout, sometimes with sclerosis
- Often richly vascular (focally pericytomatous pattern)
- Low mitotic count
- Characteristically CD34+ (but not entirely specific, and has to be interpreted in the appropriate context)

Solitary fibrous tumor (a benign neoplasm) may be mistaken for:

- Fibrosarcoma (due to high cellularity in focal areas)
- Synovial sarcoma (due to high cellularity in focal areas)
- Peripheral nerve sheath tumor
- Hemangiopericytoma
- Desmoplastic mesothelioma for tumors occurring in the pleural cavity (desmoplastic mesothelioma, in contrast to solitary fibrous tumor, is CK+ CD34-)

Tumors related to solitary fibrous tumor

Mammary myofibroblastoma

- Very similar to solitary fibrous tumor in histology, except for presence of slightly more cytoplasm
- Also CD34+
- Differs in showing more myoid features (often actin/desmin +)

Spindle cell lipoma

- There is some morphologic similarity between solitary fibrous tumor and spindle cell lipoma (spindle cells and thick collagen fibers)
- Both show CD34 reactivity

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Lymphoid Lesions of the Thyroid (Cases 14 - 15)

CASE 14

Salient histologic features

- Dense lymphoid infiltrate
- Medium-sized lymphoid cells with pale cytoplasm, mixed with some large cells (some slides may have focal areas showing an appreciable number of large cells)
- Invasion of follicles by lymphoid cells
- Thyroid follicles with oxyphilic changes
- Some residual lymphoid follicles

Immunohistochemistry (case 14)

- L26 (CD20) +
- CD3 -
- MT1 (CD43) -
- Kappa light chain -
- Lambda light chain +

That is, the abnormal lymphoid cells are of B-lineage and are furthermore shown to be monotypic.

Diagnosis

Thyroid -- **Low grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) [extranodal marginal zone B cell lymphoma] with increased large cells, arising in a background of Hashimoto's thyroiditis**

Why classify it as MALT lymphoma?

- Residual lymphoid follicles (which can be well highlighted by immunohistochemical staining for follicular dendritic cell markers) present in the background
- Mixture of lymphoid cells (monocytoid B cells, plasma cells, large activated cells)
- Tendency to invade thyroid follicles, forming lymphoepithelial lesions

Low grade B-cell lymphoma of MALT

Terminology

- In the REAL classification, it is known as "extranodal marginal zone B cell lymphoma".
- MALT lymphoma is so named because of similarities to architecture/cytology of lymphoid tissues of the mucosa (either naturally present or acquired in autoimmune disease or inflammation). In the case of the thyroid, Hashimoto's thyroiditis provides the commonest soil upon which MALT lymphomas arise.
- Previously often mistaken for pseudolymphoma.
- Previously if diagnosed as lymphoma, often mistakenly thought to represent a follicle center cell lymphoma (centroblastic-centrocytic lymphoma).

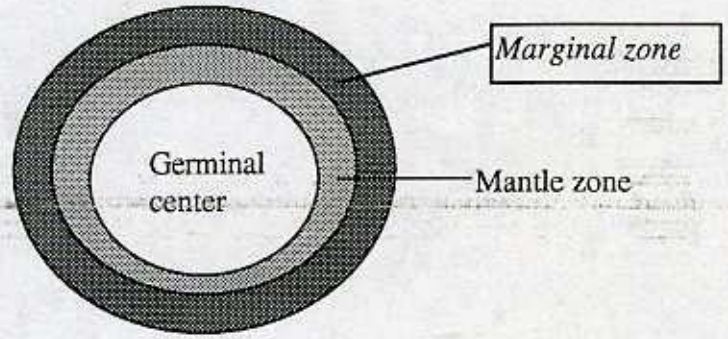
Typical histologic features of low grade B-cell lymphoma of MALT

- Small to medium-sized cells (centrocyte-like cells, small lymphocytes, monocytoid B cells) growing diffuse and in a perifollicular pattern. The cytologic features can be quite variable from case to case.
- Invasion of epithelium to produce lymphoepithelial lesions.
- May show plasma cell differentiation.
- Scattered reactive lymphoid follicles commonly present.
- The follicles may be colonized by the lymphoma cells. This may lead to mimicry of follicular lymphoma.

Evidence supporting that low-grade B-cell lymphoma of MALT is a neoplasm of marginal zone B cells

Morphologic	• Marginal zone (perifollicular) growth pattern in the primary tumor • Selective involvement of the marginal zones of lymphoid follicles in the regional lymph nodes and spleen when these sites are involved
Immunologic	• Lack of expression of CD5 (positive in small lymphocytic and mantle cell lymphoma) • Lack of staining for CD23 (positive in small lymphocytic lymphoma) • Lack of expression of cyclin D1/bcl-1 (positive in mantle cell lymphoma) • Lack of expression of CD10 (commonly expressed in follicular lymphoma) • Immunophenotypic similarity to marginal zone B cells (predominantly CD5-, IgM+, IgD-)
Genotypic	• Lack of *bcl*-1 gene rearrangement as typical of mantle cell lymphoma • Lack of *bcl*-2 gene rearrangement as typical of follicular lymphoma • Somatic hypermutation of Ig gene indicating an antigen selection process, consistent with a post-germinal center stage of differentiation, and similar to normal marginal zone B cells

Furthermore, >60% of low grade B-cell lymphoma of MALT exhibit a distinctive chromosomal aberration, Trisomy 3. The evidence is therefore very strong that this is a marginal zone B-cell lymphoma.



Low grade B-cell lymphoma of MALT: general features

- Commonest sites of involvement: gastrointestinal tract, salivary gland, thyroid, lung
- Presentation: Mass lesion; nonspecific symptoms; or incidental finding
- Typically localized to involved organ and/or regional lymph nodes for a long time before dissemination occurs (if it really does).
- 79% of cases have stage I/II disease at presentation.
- Thus, many can be treated (cured) by locoregional therapy.
- Complete remission rate: ~72%.
- Very favorable prognosis (the best prognosis among the various lymphoma types).
- For the reason of the localized nature and very good prognosis, it is most important to recognize this lymphoma type. A major differential diagnosis is mantle cell lymphoma (much more aggressive), which can also involve the thyroid as part of disseminated disease. Mantle cell lymphoma is often CD5+ and cyclin D1+.

Some biologic properties of low grade B-cell lymphoma of MALT that may cause problems in management

Multicentricity

- It is not uncommon for the lymphoma to involve multiple separate foci in the organ.
- This is sometimes a problem for the gastric lymphomas, because multicentric tumor can be found in the resection margin. This is less of a problem in the thyroid if total thyroidectomy is performed.

Aberrant homing pattern

- There is a tendency for aberrant "homing" of the lymphoma to other mucosal sites, either synchronously or metachronously.
- A tumor that starts off in the thyroid may subsequently develop disease in the gastrointestinal tract, and vice versa.
- Therefore surveillance of the gastrointestinal tract is sometimes recommended for patients with thyroid lymphoma.

Large cell (high grade) transformation

- Low grade B-cell lymphoma of MALT, if left untreated, can potentially transform to a diffuse large B cell lymphoma. The magnitude of this risk is not known, and is at least 9% according to a recent study from France (Berger et al).
- The prognostic implication of this event is controversial, but there are recent studies (at least for the stomach) that this occurrence worsens the prognosis.
- The criteria for diagnosis of large cell transformation have not been well defined. The mere presence of some interspersed large cells is not adequate for such a designation -- in fact such cells are very common in low grade B cell lymphoma of MALT. Some studies use a percentage criterion, but I adopt the following: *presence of tight clusters or sheets of large cells* (signifying a transformation process).
- Admittedly there must be borderline situations when it is difficult to judge if large cell transformation has taken place. Terms such as ".... with increased large cells" may be used in such circumstances.

Lymphomas of the thyroid

- Among the primary lymphomas of the thyroid, Hodgkin's disease is extremely rare or practically nonexistent.
- Diffuse large B cell lymphoma and low grade B cell lymphoma of MALT account for practically all cases, with the former outnumbering the latter.
- They almost always arise in a background of Hashimoto's thyroiditis or lymphocytic thyroiditis.
- Some patients present with slow enlargement of the thyroid, while others present with rapid enlargement of the gland. [Most cases diagnosed in the past as small cell type of anaplastic thyroid carcinoma represent malignant lymphoma.]
- Low grade B-cell lymphoma of MALT definitely has a superior outcome compared with the diffuse large B cell lymphomas.

How to recognize or when to suspect early lymphoma in Hashimoto's thyroiditis?

- Dense lymphoid and/or plasmacytic infiltrate (which can be focal)
- Significant number of lymphoid cells with pale or clear cytoplasm ("monocytoid B cells")
- Florid lymphoepithelial lesions

What can be done to confirm the suspicion of lymphoma?

- Demonstration of immunoglobulin light chain restriction: this is most useful. Since plasma cell differentiation is not uncommon and there are also plasmacytoid cells, this feature usually not difficult to demonstrate.
- Immunostaining for B and T cell markers:
  - ◊ Presence of diffuse dense sheets of B cells outside the lymphoid follicles is strongly supportive of a diagnosis of lymphoma.
  - ◊ Coexpression of B and T cell markers (especially CD43) is another supportive feature.

- Molecular analysis: If the above results are equivocal, molecular analysis can be applied. Polymerase chain reaction can be applied on routine paraffin embedded materials for demonstration of clonal immunoglobulin gene rearrangements.

CASE 15

Why isn't this case simply an example of Hashimoto's thyroiditis?

- There is no oxyphilic change in the follicular epithelium
- There are many psammoma bodies, which are practically pathognomonic of papillary carcinoma
- Careful search reveals small islands of tumor hiding within the inflammatory background.

The prominent knife-marks are an important clue! (They result from the calcified psammoma bodies, which are hard to cut.)

Diagnosis

Thyroid -- **Papillary carcinoma, diffuse sclerosing variant**

Diffuse sclerosing variant of papillary thyroid carcinoma

- Typically affects children and young adults
- Unilateral/bilateral symmetrical thyroid swelling
- May have detectable anti-thyroglobulin and anti-microsomal antibodies in serum, and thus coupled with the finding of diffuse thyroid swelling, may be mistaken on clinical grounds to represent thyroiditis
- This variant of papillary carcinoma is considered to be more aggressive (with more frequent lymph node and distant metastasis), but the overall survival rate is no different from that of typical papillary carcinoma (perhaps related to the young age of the patients, which is a favorable prognostic factor)

Key histologic features of the diffuse sclerosing variant of papillary carcinoma

- *Diffuse* involvement of one or both lobes
- Extensive sclerosis
- Heavy lymphoplasmacytic infiltration, often with lymphoid follicles
- Dispersed small islands of papillary carcinoma (which often show extensive squamous differentiation)
- Numerous psammoma bodies
- Prominent lymphatic permeation

* The mere presence of multiple small islands of papillary carcinoma which are accompanied by sclerosis in the vicinity does not qualify for this variant.

Problems in diagnosis the diffuse sclerosing variant

- Inflammatory background may lead to an erroneous diagnosis of thyroiditis
- The small islands of carcinoma hiding among the inflammatory cells and residual thyroid follicles may be totally missed
- Even if one can identify the tiny islands of carcinoma, it may be difficult to recognize it as being papillary carcinoma due to the prominent squamous differentiation (nuclear features typical of papillary carcinoma are not evident in such foci). The best clue that the tumor represents papillary carcinoma is the presence of psammoma bodies.

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Assessment of Parathyroid Neoplasms (Cases 16 - 17)

PARATHYROID NEOPLASMS: ASSESSMENT

Problems in assessment

1. Parathyroid adenoma or parathyroid hyperplasia?
2. Parathyroid adenoma or parathyroid carcinoma?
3. Recognition of parathyroid nature of a neoplasm in an ectopic site, e.g. thyroid, anterior mediastinum

Parathyroid adenoma or parathyroid hyperplasia?

Causes of parathyroid hyperplasia

1. Primary (need to exclude multiple endocrine neoplasia)
2. Secondary, e.g. chronic renal failure

Recognition of parathyroid hyperplasia

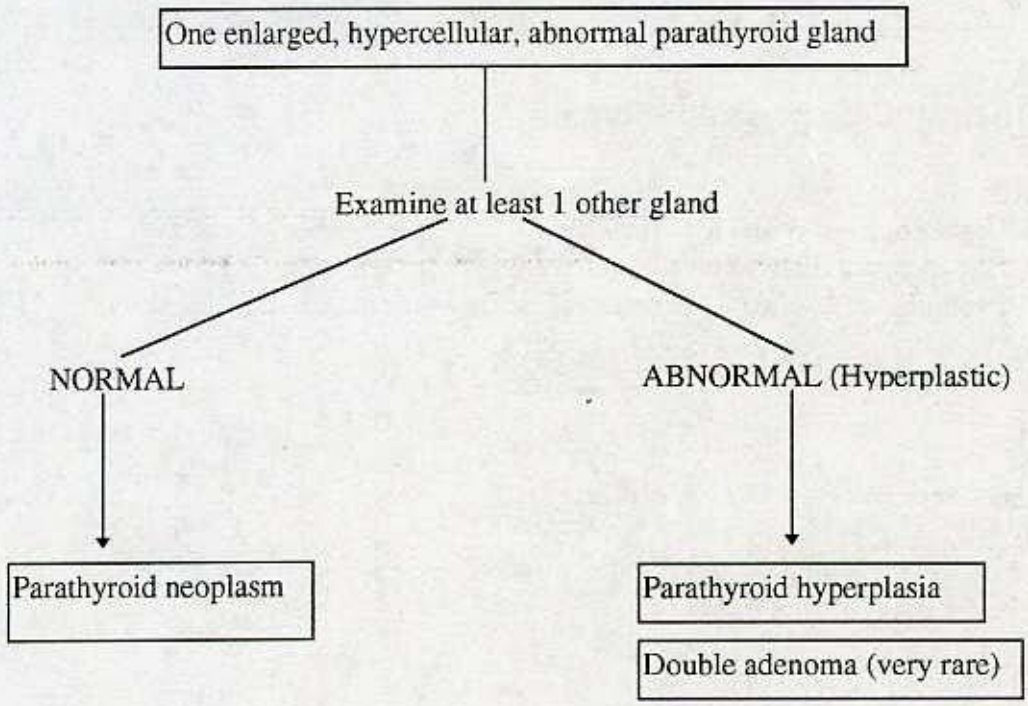
- Although the initial phase is diffuse, the process eventually becomes nodular.
- Thus a multinodular pattern strongly favors a diagnosis of parathyroid hyperplasia (although rarely adenoma may supervene on the nodular hyperplasia).
- The process typically involves all the parathyroid glands, although the individual glands may be involved to different degrees (i.e. some glands may be larger than the others)

How to tell between parathyroid adenoma and hyperplasia?

- Identification of an atrophic rim of parathyroid tissue favors a diagnosis of parathyroid neoplasm. The atrophic parathyroid tissue can be recognized by the smaller size of the cells and the smaller size of the nuclei.
- However, lack of the atrophic rim of parathyroid tissue does not rule out the possibility of parathyroid adenoma.
- Also one has to be cautious that the compressed intervening normal parenchyma in nodular hyperplasia may mimic the atrophic rim of parathyroid tissue.

* Parathyroid adenoma is treated by excision of the involved gland, while parathyroid hyperplasia is treated by excision of 3.5 glands.

The approach:



How to recognize that a parathyroid gland is hypercellular (abnormal)?

- Any gland weighing >60 mg
- Obviously enlarged gland (versus a normal size of up to 6 x 4 x 2 mm)
- Complete absence of fat cells in the gland [Potential problem: lipoadenoma, but such glands are obviously enlarged]
- Parathyroid cells larger than normal
- Absence of cytoplasmic lipid droplets, as demonstrated by fat stain

Distinction between parathyroid adenoma and parathyroid carcinoma

Parathyroid adenoma

- Curable by simple excision of the involved gland
- If the tumor recurs, consider the possibility of "missed" parathyroid carcinoma!
- Usually weighs <1 gram
- Circumscribed
- Hypercellular, with few or no adipose cells interspersed
- Vasculature: usually sinusoidal
- Secondary changes (such as fibrosis, hemorrhage, edema, infarction, cystic change) are common
- Histologically, grows in the form of solid sheets, cords, follicles and microcysts
- Chief cells, clear cells and oxyphilic cells, often a mixture
- Variable degrees of nuclear atypia can be present

Parathyroid carcinoma

- Average weight 12 grams
- Usually hard; often with thick fibrous capsule and sclerotic septa
- Usually locally invasive, but some may be encapsulated
- Nuclear atypia variable
- Often with identifiable mitotic figures
- Local recurrence after excision is common
- Metastasis develops in one-third of cases, and the metastasis is often delayed
- The commonest sites of metastases are: regional lymph node, lungs, liver, bone
- Indolent; patients may survive many years despite recurrence or metastasis.
- 5-year survival: 44-69%
- Death is usually attributable to metabolic complications rather than tumor mass replacing organ-tissues.
- The best chance for obtaining a cure is an adequate en-bloc excision in the first surgical operation. (That is why it is important to treat as for parathyroid carcinoma if the clinical or operative findings are suspicious.)
- With recurrence, usually not possible to cure (although surgery may be effective in palliating symptoms)
- Radiation and chemotherapy usually not effective

	Parathyroid adenoma	**Parathyroid carcinoma**
Incidence	Much higher (>85% of primary hyperparathyroidism)	Rare (1-5% of primary hyperparathyroidism)
Sex	F > M	F = M
Age	Mean 56 years	Mean 46 years
Asymptomatic	12-50%	Very rare
Renal involvement	4-30%	48%
Skeletal involvement	14-20%	63%
Hypercalcemia	Present	More severe

The difficulties in distinction between parathyroid adenoma and parathyroid carcinoma

- In some circumstances, distinction between parathyroid adenoma and parathyroid carcinoma is straight-forward.
- But in some instances, a distinction can be very difficult to make: there is marked morphologic overlap between the two. Another feature that contributes to the difficulties is that parathyroid carcinomas are very indolent, and the true nature of a parathyroid neoplasm may not be evident on short-term follow-up.
- Some parathyroid adenomas can show marked cytologic atypia.
- On the other hand, some parathyroid carcinomas are deceptively bland-looking.

Assessment: parathyroid adenoma or carcinoma?

- Constellation of features need to be considered:
  - ◊ Clinical
  - ◊ Operative findings
  - ◊ Histologic features
  - ◊ Ancillary studies
- Histologic criteria of malignancy proposed by Schantz and Castleman:
  - ◊ Mitotic figures in parenchymal cells (not in endothelial cells)
  - ◊ Thick fibrous bands
  - ◊ Capsular invasion
  - ◊ Vascular invasion
  - ◊ Trabecular growth pattern
- Histologic criteria proposed by Evans:
  - ◊ Thick fibrous capsule with capsular invasion
  - ◊ High mitotic count >5/10 HPF

Although presence of mitotic figures were emphasized by Schantz and Castleman to be very important, others have identified occasional mitotic figures in parathyroid hyperplasia or parathyroid adenoma. Mitotic figures have to be frequent before they are significant, but of course presence of mitotic figures should lead to careful assessment for possibility of malignancy.

Clues for recognizing parathyroid carcinoma (versus parathyroid adenoma)

Clinical clues	Clues at operation
• Very high serum calcium level (>3.5 mmol/L or 14 mg/dL) • Simultaneous parathyroid bone disease and renal stone • Palpable neck mass • Vocal cord paralysis • Presence of metastasis	• Firm consistency • Thick capsule • Adherence and invasion to adjacent organs, e.g. thyroid, muscle, nerve, esophagus

* The clinical clues actually reflect a large size tumor or a tumor with invasive properties.

My approach in assessment of malignancy in parathyroid neoplasm

Absolute criteria of malignancy	**Features associated with malignancy**
Presence of any one of the following criteria is sufficient for a diagnosis of malignancy	*At least 2, preferably 3 or more, of the following features have to be present in order to establish a diagnosis of malignancy*
1. Invasion into surrounding tissues • Thyroid • Esophagus • Nerves • Soft tissues 2. Histologically documented regional or distant metastasis	1. Capsular invasion: transgression of fibrous capsule 2. Vascular invasion: assess as for follicular neoplasm of thyroid 3. Readily identifiable mitotic figures (>5/10 HPF) 4. Broad intratumoral fibrous bands splitting the parenchyma and separating expansile nodules 5. Coagulative tumor necrosis (to be distinguished from infarction, which can also occur in parathyroid adenoma) 6. Diffuse sheet-like monotonous small cells with high N/C ratio 7. Diffuse cellular atypia

Ancillary techniques to aid in recognition of malignancy in parathyroid neoplasm

- Ploidy analysis: Not too useful, because there is overlap between parathyroid carcinoma and parathyroid adenoma (both can be aneuploid)
- Proliferative fraction: Potentially useful (carcinoma has significantly higher proliferative index than adenoma: mean Ki67 index being 3.28% for adenoma, and 7.86% for carcinoma)
- Allelic loss of *Rb* gene: found in 100% of carcinomas, and only 5% of adenomas. Can be demonstrated by loss of immunoreactivity for *Rb* protein (endothelial cells serving as internal positive controls) or by molecular analysis. Since some parathyroid adenomas show overexpression of cyclin D1 (*PRAD1*) as a result of chromosomal inversion, and development of parathyroid carcinoma is associated with loss of Rb function, it appears that genes controlling the restricted point of the cell cycle are important in the genesis of parathyroid neoplasm.

	Case 16	Case 17
Serum calcium	10.9 - 11.6 mg/dL	12.4 mg/dL
Symptoms of bone disease	Yes	Yes
Neck mass	?	Yes
Vocal cord paralysis	No	Yes
Weight	1 g	24 g
Absolute criteria of malignancy	None	None
Capsular/vascular invasion	No	No
Mitotic figures	No	Some (esp. when highlighted with Ki-67 antibody)
Fibrous bands	No	No
Coagulative necrosis	No	No
Sheet-like small cells	No	Focal

CASE 16

Salient findings

- No ominous features clinically or at operation
- Histologically, there are no invasive features.
- Although there are some groups of cells with large hyperchromatic or bizarre nuclei, mitotic figures are not seen. (This feature is not incompatible with a benign diagnosis.)

Immunohistochemistry

- Cytokeratin (CAM5.2) +
- Chromogranin +
- Synaptophysin +
- Ki-67: very few positive cells

Diagnosis:

Parathyroid gland -- **Parathyroid adenoma**

CASE 17

Salient findings

- Clinically, there are two features highly suspicious of malignancy:
    1. Vocal cord paralysis
    2. Palpable neck mass
- Histologically, although there is no evidence of invasion, there are some suspicious features:
    - ◊ Focal areas with monotonous cells having high N/C ratio (in addition to presence of bizarre cells)
    - ◊ Foci of spindly cells
    - ◊ Some mitotic figures (although nothing near the threshold of 5/10 HPF)

Immunohistochemistry

- Cytokeratin (CAM5.2) + [including the spindle cell foci]
- Chromogranin + [including the spindle cell foci]
- Synaptophysin +
- Ki67: More positive cells than in Case 16; also highlighting the cells in mitoses (not obvious in routine H&E stain)

Diagnosis

Parathyroid gland -- **Parathyroid neoplasm of uncertain malignant potential, with an unusual spindle cell component**

[Spindle cell component is extremely uncommon in parathyroid neoplasms, but this phenomenon has also been documented in the literature.]

A diagnosis of "uncertain malignant potential" is applied here instead of "parathyroid carcinoma" because there are not sufficiently convincingly histologic features of malignancy. This designation is used in recognition of the clinically suspicious features plus some unusual histologic features. Furthermore, although mitotic figures are not obvious in H&E sections, sections with a lighter hematoxylin stain (such as PAS stain) show up some mitotic figures, and Ki-67 immunostaining shows up even more.

How to recognize ectopic parathyroid tumors?

The problem

- Parathyroid adenoma in the thyroid may mimic follicular adenoma or Hurthle cell adenoma, especially since follicles may be present.
- Parathyroid carcinoma may be mistaken for anaplastic thyroid carcinoma when it invades the thyroid, but the prognosis is very different! (Indolent for parathyroid carcinoma, but highly aggressive for anaplastic thyroid carcinoma.)

When to suspect parathyroid neoplasm in the thyroid?

- Mixture of cell types (clear cells, oxyphilic cells, lightly basophilic cells)
- Many cells with water-clear cytoplasm
- Oxyphilic cells with discrete cell membrane (cell membrane of oxyphilic/Hurthle cells of the thyroid usually do not possess discrete cell membrane)
- Relatively few mitotic figures in an "anaplastic thyroid carcinoma"

How to confirm the parathyroid nature of the neoplasm?

- Check serum calcium
- Chromogranin positive
- Parathyroid hormone positive

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Assessment of Adrenocortical Neoplasms (Cases 18 - 19)

PROBLEMS IN DIAGNOSIS OF ADRENOCORTICAL NEOPLASMS

- It can be difficult to predict the behavior of some adrenocortical neoplasms.
  - ◊ Although some adrenocortical carcinomas are obviously malignant histologically, some may be bland-looking.
  - ◊ Some small tumors can metastasize, while some large tumors have benign outcome.
  - ◊ Pleomorphic cells can be seen in perfectly benign adrenocortical adenomas.
- Some adrenocortical carcinomas can be difficult to distinguish from pheochromocytomas.
- May be difficult to recognize adrenocortical nature of adrenocortical carcinomas presenting initially as large retroperitoneal mass.

Adrenocortical adenoma

- Solitary nodule (Differential diagnosis: adrenocortical nodule, which is a very common autopsy finding, especially in older subjects.)
- Cytoarchitecturally resembles normal adrenal cortex (trabeculae and packets).
- Usually mixture of cell types: compact cells, clear vacuolated cells, oxyphilic cells. Any of these cells types may predominate in an individual case.
- There can be scattered large atypical cells with pleomorphic or bizarre nuclei.
- A rare variant is *oncocytoma*: composed entirely of oncocytes; such tumors are often of large size.
- Commonest functional status:
  - ◊ Cushing's syndrome
  - ◊ Conn's syndrome
  - ◊ Non-functional
  - ◊ Less commonly, symptoms due to sex hormone production
- Curable by excision.

Adrenocortical carcinoma

Clinical features

- Wide age range, mean 47 years
- Slight female predominance
- Produce hormonal symptoms
- Tumors often large: mean weight 714 grams (larger for non-functional tumors)
- Often advanced stage disease at presentation (~50%)

Scoring systems for the assessment of adrenal cortical neoplasms

Weiss	Hough et al.		Van Slooten et al.	
Histologic criteria	Histologic criteria	Score	Histologic criteria	Score
1. High nuclear grade	1. Diffuse growth pattern	0.92	1. Extensive regressive changes (necrosis, hemorrhage, fibrosis, calcification)	5.7
2. Mitotic rate greater than 5/50 HPF*	2. Vascular invasion	0.92	2. Loss of normal structure	1.6
3. Atypical mitotic figures	3. Tumor cell necrosis (>2HPF in diameter)	0.69	3. Nuclear atypia (moderate/marked)	2.1
4. Eosinophilic tumor cell cytoplasm (≥75% of tumor cells)	4. Broad fibrous trabeculae (>1HPF in diameter)	1.00	4. Nuclear hyperchromasia (moderate/marked)	2.6
5. Diffuse architecture (≥33% of tumor)	5. Capsular invasion	0.37	5. Abnormal nucleoli	4.1
6. Necrosis	6. Mitotic index (>1 per 10 HPF)*	0.60	6. Mitotic activity [>2/10 HPF(x400)]	9.0
7. Venous invasion (smooth muscle in wall)	7. Pleomorphism (moderate/marked)	0.39	7. Vascular or capsular invasion	3.3
8. Sinusoidal invasion (no smooth muscle in wall)				
9. Capsular invasion	Non-histologic criteria	0.60		
	1. Tumor mass (>100g)	0.50		
	2. Urinary 17-ketosteroids (>10mg/g creatinine/24hours)	0.42		
	3. Lack of response to ACTH	0.42		
	4. Cushing's syndrome with virilism, virilism, or no clinical manifestations	2.00		
	5. Weight loss (>10 lb/3 months)			
Criteria of malignancy: Presence of *any three or more* of the above criteria	Criteria of malignancy: **Not explicitly stated; but mean *histologic* value for malignant, indeterminate and benign tumors are 2.91, 1.00 and 0.17 respectively**		Criteria of malignancy: **Score for malignant tumor ≥ 8** **Score for benign tumor < 8**	

HPF = high power field. In the system of Weiss, 10 HPF in each of five areas with highest mitotic count are assessed to give a mitotic count per 50 HPF. In Hough et al., the average mitotic count in 100 (presumably random) HPF is counted and divided by 10 to give the mitotic index (per 10 HPF). The details of mitotic figure counting was not specified by Van Slooten et al..

Behavior

- High frequency of metastasis
- Sites of metastasis: lung, retroperitoneal lymph nodes, liver, bone
- 5-year actuarial survival: 34% (related to stage)
- Long-term survival: ~10%
- Deaths caused by metastatic tumor usually occur within one year

The various endocrine/neuroendocrine carcinomas of various organs/sites are usually indolent. Adrenocortical carcinoma is one of the few that are highly aggressive.

Features favoring a diagnosis of adrenocortical carcinoma over adenoma

Clinical-Biochemical Features	Histologic features
Related to a large tumor • Palpable mass; rapid increase in size • Abdominal pain; weight loss • Fever (? tumor necrosis) • Large tumor on imaging (>6 cm) • Heavy tumor (>100 grams) • Prominent secondary changes (hemorrhage, necrosis) *Uncommon endocrine activities* • Mixed (rather than pure) endocrine syndromes • Feminization or virilization • Non-functional tumor • Increased urine 17-ketosteroids	*Invasion:* • Vascular invasion • Capsular invasion *Diffuse growth*: Lacking packets/trabeculae *Cytology*: • Compact cells predominating • Increased N/C ratio • Generalized cellular atypia • High mitotic count • Atypical mitoses

How well do the various scoring systems work for diagnosis of adrenocortical carcinoma?

- Any one system works very well
- However, it should be remembered that not every case assigned to the "malignant" category has a malignant outcome.
- That is, using these systems, false negative diagnosis is rare.
- From these scoring systems, several features are incorporated in all of them, suggesting that they are very important:
  1. Vascular invasion
  2. High mitotic count
  3. Coagulative necrosis

Special points to note in diagnosing malignancy in adrenocortical neoplasms

- Search for other ominous features whenever mitotic figures are seen.
- Some cases may show one or two ominous features only, but do not distinctly fall into the "carcinoma" category, may apply the term "*adrenocortical neoplasm of uncertain malignant potential*".

Value of ancillary studies in recognition of malignancy in adrenocortical neoplasms

- Ploidy: Not helpful
- Ki-67 score (Intensity x Extent positivity): score >50 is usually associated with adverse outcome

Immunohistochemistry of adrenocortical neoplasm

- Cytokeratin: Normal adrenal cortex and adrenocortical adenoma usually positive; cytokeratin reactivity usually lost in carcinoma (but results are variable)
- EMA: Negative
- Neuroendocrine markers (such as chromogranin, synaptophysin, neurofilament, neuron specific enolase): Normal adrenal cortex and adrenocortical adenoma are negative. But some adrenocortical carcinomas may show reactivity for synaptophysin, neurofilament or neuron specific enolase (but not chromogranin).

There are some common themes for recognition of malignancy in both parathyroid and adrenocortical neoplasms:

- Large tumor size and related effects
- Invasion of capsule or blood vessels
- Broad fibrous bands
- Diffuse architecture (loss of packeting or trabecular pattern)
- High mitotic count
- Coagulative necrosis

CASE 18

Using any of the grading systems (such as large tumor size, cellular atypia, compact cells, mitotic figures, focal diffuse pattern, vascular invasion, coagulative necrosis, broad fibrous bands), this case would have to be considered malignant.

Adrenal gland -- **Adrenocortical carcinoma**

[In this case, more cells are Ki-67 positive than in case 19.]

CASE 19

Using any of the grading systems, this case is definitely benign.

Adrenal gland -- **Adrenocortical adenoma**

RECOGNITION OF ADRENOCORTICAL CARCINOMA VERSUS OTHER TUMORS

Sometimes adrenocortical carcinoma presents initially as a retroperitoneal mass. The adrenocortical nature of the neoplasm may not be suspected at all. Important differential diagnoses are:

- Adrenocortical carcinoma
- Renal cell carcinoma
- Metastatic carcinoma from other sites
- Paraganglioma
- Metastatic melanoma

Histologic clues

- Clear cells (often mixed with some cells with eosinophilic cytoplasm)
- Trabecular pattern
- Sinusoidal vascular pattern

Confirmation of adrenocortical nature

- Cytokeratin -/+, EMA - (vs. renal cell carcinoma, which is usually EMA+ and which often has some glands)
- Chromogranin - (vs pheochromocytoma)
- Very helpful and highly diagnostic: Mitochondria with tubular cristae; abundant smooth endoplasmic reticulum

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Miscellaneous Neural and Neuroendocrine Tumors of Various Sites (Cases 20 - 24)

CASE 20

Salient histologic features

- Circumscribed tumor
- "Dirty"-look (a very common feature and diagnostic clue for pheochromocytoma)
- Neural/neuroendocrine look:
  - ◊ Packets
  - ◊ Delicate vasculature
  - ◊ Large cells with granular cytoplasm
- Scattered gigantic cells
- Hyaline globules (D-PAS positive) in cytoplasm (a common finding in pheochromocytoma)

Immunohistochemistry

- Cytokeratin -
- Chromogranin +
- Synaptophysin +
- S100 protein: focally some sustentacular cells

Diagnosis

Adrenal gland -- **Pheochromocytoma**

Pheochromocytoma

- A form of paraganglioma
- Considered a "neural" form of tumor (i.e. cytokeratin negative, neuroendocrine markers positive)
- The "10%" tumor:
  - ◊ 10% bilateral
  - ◊ 10% extraadrenal (paraganglioma with clinical evidence of norepinephrine or epinephrine secretion)
  - ◊ 10% children
  - ◊ 10% malignant
- Amyloid may be present in some cases

Immunohistochemical profile of pheochromocytoma (the same as for paraganglioma)

- Cytokeratin -
- Chromogranin/Synaptophysin +
- S100 protein: Usually demonstrating sustentacular cells that surrounded the individual packet sof tumor cells, although these cells can be sparse or markedly attenuated. Sustentacular cells can also be seen in olfactory neuroblastoma, some neuroblastomas and some carcinoids. That is, while S100+ sustentacular cells are characteristic of pheochromocytoma, they are by no means pathognomonic.

Can one predict the "bad actors" among the pheochromocytomas?

- Very difficult
- Presence of cellular atypia is not synonymous with a diagnosis of malignancy
- The only foolproof criterion of malignancy is *presence of metastasis*.
- *Frank invasion of adjacent major organs* can also be considered a feature of malignancy.
- The presence of the following features should raise concern for metastatic potential (but are by themselves not diagnostic of malignancy):
    1. Coagulative necrosis
    2. Mitotic activity
    3. Vascular invasion
    4. Absence of S100+ sustentacular cells
- It has also been suggested DNA ploidy may have a predictive value for outcome (none of the patients with diploid DNA die from tumor, while 95% of patients with disease progression have abnormal DNA ploidy pattern such as tetraploidy or aneuploidy).

Behavior of the malignant pheochromocytomas

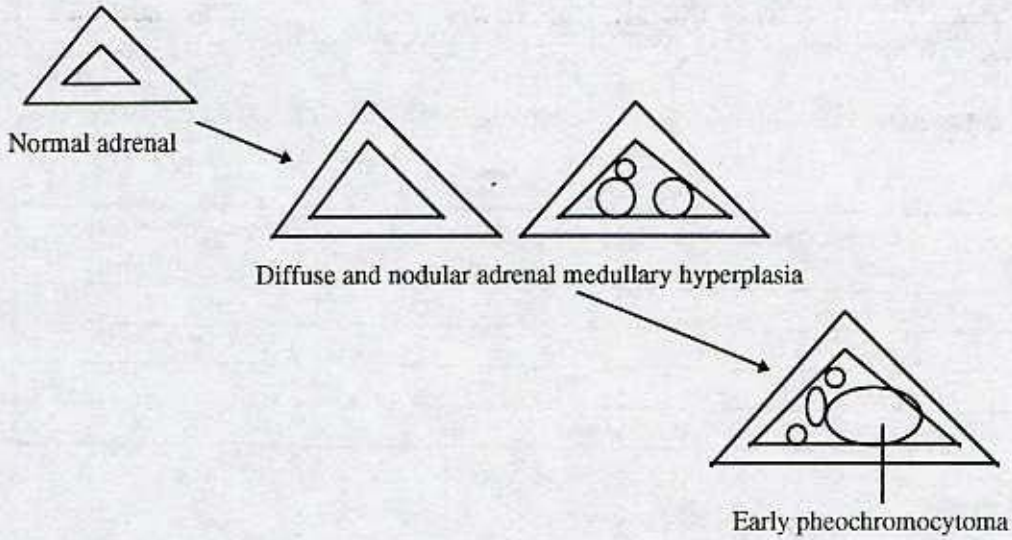
- Local recurrence
- Distant metastasis, with a propensity for bones (ribs, spine)
- Metastatic disease: often die within one year
- Locally invasive disease: may have long-term relapse-free survival

Clinical implications of a diagnosis of pheochromocytoma

- Associations:
    - ◊ MEN IIa, MEN IIb
    - ◊ Neurofibromatosis
    - ◊ von Hippel-Lindau disease
    - ◊ Renal artery dysplasia
- These possibilities have to be considered, in particular von Hippel-Lindau disease and MEN II (clinical history helpful; *RET* gene analysis)

Hereditary form of pheochromocytoma (MEN II)

- Younger age of onset
- More commonly bilateral
- More commonly associated with other primary neoplasms
- Arising in a background of adrenal medullary hyperplasia (diffuse and/or nodular) [Nodules >1 cm are arbitrarily considered pheochromocytoma]



CASE 21

Salient histologic features

- Circumscribed tumor
- Neural/neuroendocrine-look:
  - ◊ Packets (Zellballen pattern)
  - ◊ Delicate vasculature
  - ◊ Granular cytoplasm
- Isolated large atypical cells

Immunohistochemistry

- Cytokeratin -
- Synaptophysin +
- Chromogranin +
- S100 protein: +ve sustentacular cells

Diagnosis

Soft tissue -- **Paraganglioma** (carotid body tumor; chemodectoma)

What is paraganglion?

- Paraganglia form a widely disseminated system of small sensory/neurosensory organs (including chemoreceptors)
- Distributed in relationship to autonomic nervous system
- All paraganglia store catecholamines
- Families of paraganglia:
  - ◊ Branchiomeric/intravagal (parasympathetic): Juglulotympanic (middle ear), nasopharynx, carotid body, larynx, thyroid, aortico-pulmonary
  - ◊ Aortico-sympathetic: Intrathoracic-paravertebral, retroperitoneum, organs of Zuckerkandl
  - ◊ Visceral-autonomic: Gastroduodenal, porta hepatis, genitourinary, cauda equina

	Pheochromocytoma	**Sympathetic paraganglioma**	**Parasympathetic paraganglioma**
Epinephrine	+++	+	-
Norepinephrine	+++	++	+
5-hydroxy-tryptamine	+/-	-	+
Hypertension	++++	++	+/-

Paraganglioma: clinical associations

- Multifocal in 2-5%
- Some cases are familial
- Pheochromocytoma (adrenal paraganglioma) associated with MEN II
- Extraadrenal paraganglioma may occur as a component of Carney's triad
- von Hippel-Lindau disease

Paraganglioma: Clinical behavior

- Most are curable by excision
- Jugulotympanic tumors are locally invasive
- Approximately 10% are malignant, with regional or distant metastasis (often delayed)
- Intraabdominal extraadrenal paragangliomas have a higher risk of malignancy (20-50%)

Can one accurately predict the "bad actors" among paragangliomas?

- The metastasizing (malignant) paragangliomas cannot be reliably predicted from histologic examination.
- Some features are associated with higher risks:
  - ◊ Lack of S100+ sustentacular cells (most useful)**
  - ◊ Broad sheets of pleomorphic, mitotically active cells
  - ◊ Confluent necrosis

Problems in diagnosis of paraganglioma

To make this diagnosis, *a packeting pattern and a prominent vasculature must be present, and such features must be well developed at least in focal areas* (although some foci may show a more diffuse sheet-like growth).

- In thyroid, may mimic:
  - ◊ Medullary carcinoma
  - ◊ Hyalinizing trabecular adenoma
- In urinary bladder, may be mistaken for invasive transitional cell carcinoma, especially in small biopsies
- In soft tissues, may be mistaken for various sarcomas, e.g. alveolar soft part sarcoma
- In middle ear, may be mistaken for hemangioma

Paraganglioma versus carcinoid (Differential diagnosis)

	Paraganglioma	**Carcinoid**
Growth patterns	Packets, occasionally sheets; almost never trabecular; never glandular	Islands, trabeculae, packets, glands
Vasculature	Sinusoidal or fibrovascular	Fibrovascular
Sustentacular cells (S100+)	Commonly present	Usually absent, but may be focally present in some cases
Cytokeratin	Negative*	Positive

* Rare cytokeratin-positive cells do not negate a diagnosis of paraganglioma.

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CASE 22

Salient histologic features

- Partly circumscribed and partly invasive neoplasm
- Endocrine/neuroendocrine appearance:
  - ◊ Prominent fibrovascular septa
  - ◊ Islands, packets and cords
  - ◊ Stippled chromatin and granular cytoplasm
  - ◊ Focal fibrillary cytoplasm
  - ◊ Some spindly cells (a known feature in neuroendocrine tumors)
- Features of "aggressiveness" or "atypia":
  - ◊ Coagulative necrosis in centers of cellular islands
  - ◊ Diffuse cellular atypia
  - ◊ Readily identifiable mitotic figures

Immunohistochemistry

- Cytokeratin + (in the form of dots or short cell processes)
- Synaptophysin +
- Chromogranin +
- ACTH +

Diagnosis:

Thymus -- **Carcinoid tumor (atypical carcinoid tumor), with ACTH production**
[Patient alive and well at 8 years]

Typical carcinoid tumor

- Defined as neuroendocrine neoplasms similar to those commonly occurring in intestines, and excluding those occurring in endocrine organs (such as thyroid and parathyroid).
- Tumor of the diffuse neuroendocrine cell system.
- Commonest patterns: islands, trabeculae, occasionally glandular structures.
- Relatively bland nuclei.
- Typically highly vascularized (delicate fibrovascular septa).
- Behavior depends mostly on site and size.
- Favorable prognosis, but it is a malignant neoplasm, albeit of low malignant potential.

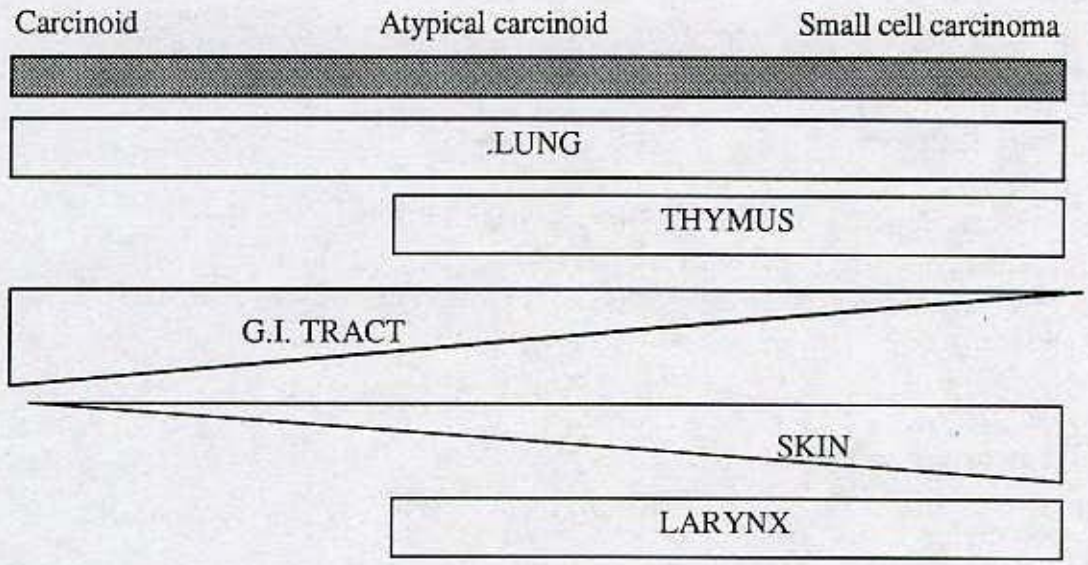
Atypical carcinoid tumor

- The term is applied to tumors with architectural features similar to carcinoid tumor, but also showing:
  - ◊ cellular atypia
  - ◊ necrosis
  - ◊ mitoses
  - ◊ increased cellularity, with more disorganized architecture.
- Compared with carcinoid, they are more aggressive, with metastatic rate in >50% of cases.

The pattern of neuroendocrine neoplasms in various organs

- A spectrum of neuroendocrine neoplasms can occur in various organs/sites: carcinoid, atypical carcinoid and small cell carcinoma, with increasing degree of aggressiveness for tumors on this spectrum. Although there are cases that show borderline features and are thus not readily classifiable into discrete categories on this spectrum, these three categories are on the whole discrete. In particular, new genetic studies suggest that small cell carcinoma is a distinct entity, and usually does not arise through transformation from a carcinoid or atypical carcinoid.
- Some have also created an additional category of "large cell neuroendocrine carcinoma" for the lung.

- Others have adopted terms such as "well differentiated", "moderately differentiated" and "poorly differentiated" neuroendocrine carcinoma for tumors in this spectrum.
- The commonest types of neuroendocrine neoplasm that occur in various organs differ remarkably, e.g. most gastrointestinal ones are typical carcinoid tumors, while most laryngeal ones are atypical carcinoid or small cell carcinoma.



Special effects of carcinoid tumors

- Carcinoid syndrome
  - ◊ For gastrointestinal carcinoid, occurs only when there is liver metastasis
  - ◊ Can develop in primary tumors if the veins of the organ drain directly into vena cava
- Other endocrine products, e.g. ACTH (such as Cushing's syndrome)
- Can produce marked fibroelastosis (narrowing of blood vessels), leading to bowel ischemia and infarction

Uncommon morphologic manifestations of carcinoid tumors

Rarely, carcinoid tumors may assume unusual histologic appearances that may lead to difficulties in recognition of the true nature of the tumor.

- Oncocytic cells
- Clear cells
- Spindly cells
- Rosettes
- Pigmented
- Squamous differentiation

- Glandular differentiation (not surprising since neuroendocrine tumors probably arise from stem cells; tumor can also show dual differentiation, e.g. goblet cell carcinoid, mixed carcinoid-adenocarcinoma)

Thymic carcinoid tumor

Clinical features

- Practically all represent "atypical carcinoid" rather than typical carcinoid, although by convention they are simply labeled "carcinoid".
- Male predominance.
- Commonest presentation:
  - ◊ Asymptomatic
  - ◊ Symptoms referable to the mass lesion, e.g. cough and chest discomfort
  - ◊ Endocrine symptoms (most often ACTH)
- They may also uncommonly occur as a component of MEN1 or MEN2a (when the behavior is more aggressive).

Pathology

- Features of atypical carcinoid
- Trabeculae or islands
- Vascularized stroma
- Polygonal cells, but sometimes spindly
- Moderate cellular atypia, and mitoses
- Some cellular islands show central coagulative necrosis

Clinical behavior

- Aggressive neoplasm
- Totally encapsulated tumors (uncommon) are potentially curable by total excision. (This patient/case 22 has a favorable outcome; the tumor is for the most part circumscribed.)
- Most tumors are locally invasive, and recurrence is very common.
- Metastasis is also common, occurring in 70% of cases.
- The metastases can be regional or distant (such as bone, skin).
- Overall mortality is >40%.

CASE 23

Salient histologic features

- Circumscribed neoplasm
- Neuroendocrine-look:
  - ◊ Gyriform trabeculae
  - ◊ High vascularity
  - ◊ Granular cytoplasm
- Stromal edema and fibrosis

Immunohistochemistry

- Cytokeratin +
- Chromogranin + (accentuated towards the vascular pole)
- Synaptophysin +

Diagnosis:

Pancreas -- Neuroendocrine neoplasm (islet cell neoplasm); this is considered **islet cell carcinoma** because of documentation of metastasis

Islet cell neoplasm

- Case 23 shows the typical morphology of islet cell neoplasm (trabecular architecture). It apparently produces gastrin, causing peptic ulcers (Zollinger-Ellison syndrome).
- The commonest type of islet cell neoplasm is insulinoma (60-80% of all cases), followed by gastrinoma (20-25% of all cases).
- The overproduction of gastrin by gastrinoma can lead to morphologic changes in the stomach:
  1. Hyperplasia of crypts or glands, i.e. increased parietal cells, and may produce giant folds; the foveolar epithelium is not hyperplastic.
  2. Peptic ulcer
  3. May be associated with neuroendocrine cell hyperplasia in the stomach, involving the enterochromaffin cells, and even multicentric small carcinoids. This presumably results from trophic effects of gastrin on the neuroendocrine cells.

Variations in morphology of islet cell tumors

- Stroma may show:
  - ◊ Edema
  - ◊ Cystic change
  - ◊ Hyalinization
  - ◊ Amyloid deposits
- Tumor cells may show:
  - ◊ Clear cells
  - ◊ Oncocytic cells
  - ◊ Mucin production
  - ◊ Psammoma bodies

Islet cell neoplasms: important clinical aspects

1. May produce complications due to the hormonal products rather the spread of the tumor itself.
2. Should also consider the possibility of MEN1 (a disorder which has been linked to chromosome 11q13; the implicated gene has yet to be identified):
   - Anterior pituitary tumor
   - Parathyroid hyperplasia / tumor
   - Islet cell tumor
   - Adrenal cortex hyperplasia or adenoma
   - Carcinoids (including thymic carcinoid)
   - Thyroid nodule / adenoma

Islet cell neoplasm: can malignant behavior be accurately predicted?

- Unfortunately, no. All islet cell neoplasms should be considered potentially malignant.
- The histology (including mitotic count) cannot reliably predict the likely outcome.
- The *only foolproof criterion of malignancy is presence of metastasis or gross invasion of adjacent organs*.
- However, even in the absence of the above features, the tumor cannot be assumed to be benign.
- Nonetheless, hormonal products can provide a reasonably helpful idea on the likelihood of malignancy:
  - ◊ Only ~10% of insulinomas are malignant.
  - ◊ ~60-80% of islet cell tumors that produce other hormones (such as gastrin, somatostatin) or non-functional ones are malignant.
- Therefore it is important to identify the group of insulinomas, for obvious reasons in prognostication.
- Islet cell carcinomas are generally indolent, and long survivals are possible.

- Some histologic features have also been shown to be associated with a higher metastatic risk:
  - ◊ Definite stromal invasion
  - ◊ Vascular invasion
  - ◊ Solid/glandular pattern rather than gyriform pattern (?)

CASE 24

Salient histologic findings
- Dense small cell infiltrate in dermis, extending to subcutis
- Diffuse growth, apparently cohesive
- Round nuclei with fine chromatin pattern
- Scanty cytoplasm
- Delicate vasculature

i.e. Small cell neoplasm

Differential diagnoses
- ◊ Merkel cell carcinoma (neuroendocrine small cell carcinoma of skin)
- ◊ Lymphoma or leukemia, especially lymphoblastic type
- ◊ Metastatic small cell carcinoma

[Other small round cell tumors, such as rhabdomyosarcoma, neuroblastoma, are not considered in view of the age.]

Immunohistochemistry
- Cytokeratin (MNF-116, CAM5.2) +ve [focally dot-like]
- Chromogranin +
- Synaptophysin +
- Neurofilament +
- Leukocyte common antigen -
- Cytokeratin 20 +

Diagnosis
Skin -- **Merkel cell carcinoma (small cell neuroendocrine carcinoma of skin)**

Outcome of patient (Case 24)
Patient was treated by surgical excision and radiation therapy to primary site and regional lymph nodes. Disease developed in the liver and abdomen (lymph nodes) at 6 months, and the patient died soon.

Merkel cell carcinoma: diagnostic problems

- Presence of trabeculae: easily recognized as carcinoma. But for those cases with diffuse growth, distinction from lymphoma difficult (esp. lymphoblastic lymphoma).
- Distinction from metastatic pulmonary small cell carcinoma is extremely difficult. Punctate staining for cytokeratin and neurofilament has been claimed to be diagnostic, but this is certainly not true! A punctate pattern of cytokeratin immunoreactivity is very commonly observed in small cell carcinomas and carcinoid tumors.

Small cell carcinoma of various sites

Pulmonary small cell CA	Highly aggressive, with only 5-10% survival
Extrapulmonary small cell CA	Also highly aggressive
Cutaneous small cell CA (Merkel cell CA)	Comparatively better prognosis: 40-60% survival

Thus a distinction is important for management purposes.

Cytokeratin 20 immunostaining helps greatly in distinguishing Merkel cell carcinoma from other small cell carcinomas

Cytokeratin 20 (CK20)

CK20 is a subtype of keratin showing restricted distribution in normal tissues:

- Gastrointestinal epithelium
- Urothelium
- Merkel cells

Staining for CK20 in small cell carcinomas of various sites

- For Merkel cell carcinoma, CK20 is positive in 97% (32/33) of cases, with positivity in almost all cells in most cases.
- For other small cell carcinomas, all are CK20 negative except:
  - ◊ Pulmonary small carcinoma in 1/37 cases (40% of cells positive)
  - ◊ Uterine cervix small cell carcinoma in 1/11 cases (10% of cells positive)
  - ◊ Salivary gland small cell carcinoma in 3/5 cases (~100% of cells positive) [At least a significant proportion of salivary gland small cell carcinomas are biologically closely related to Merkel cell carcinoma!]
- That is, the CK20 positivity rate in small cell carcinomas of miscellaneous sites except the salivary gland ones is only 2.4% (2/83).

Applicability of CK20 for diagnosis of Merkel cell carcinoma

- Merkel cell carcinomas are almost invariably CK20+
- Other small cell carcinomas are nearly always CK20-
- Used judiciously, CK20 positivity in a small cell carcinoma of uncertain origin provides a strong support for a diagnosis of Merkel cell carcinoma, especially if most tumor cells are positive.
- Similarly, in such circumstance, CK20 negativity practically rules out the possibility of Merkel cell carcinoma.

Merkel cell carcinoma of skin: clinical features

- Predominantly a disease of adults and elderly.
- Most commonly affecting the face and extremities.
- Usually appearing as reddish or violaceous nodules (the color being due to the high vascularity). May show ulceration.
- Regional lymph node metastasis is common.
- Distant metastasis may occur.
- Overall it is a fairly aggressive neoplasm (but less aggressive than pulmonary small cell carcinoma).
- Rarely, Merkel cell carcinoma may present as lymph node primary in the absence of any skin lesion.

Morphologic identification of Merkel cell carcinoma versus other small cell carcinomas

Although it is often said that Merkel cell carcinoma cannot be reliably distinguished from pulmonary type small cell carcinoma on morphologic grounds, there are indeed certain histologic features that can help in the distinction:

- Nuclei of Merkel cell carcinoma are often round and plump, rather than spindly (i.e. not "oat" cell morphology)
- Little nuclear molding; if it is present, it is at most focal
- The chromatin is more delicate and finely granular.

That is, overall the nuclei appear "fat and pale" in Merkel cell carcinoma!

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