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Introduction

- The thyroid anlage arises in the foramen cecum of the tongue and descends as part of the thyroglossal duct to the neck. The C-cells migrate to the ultimobranchial bodies from the neural crest and are incorporated into the thyroid gland. The adult thyroid gland weight is between 15 and 25 g.
- The thyroid gland is made up of lobules, which are composed of 20–40 follicles, which in tum composed of follicular cells. Follicular cells are positive for thyroglobulin, keratin, and TTF-1. The calcitonin-producing C-cells have pale to clear cytoplasm and oval nuclei, and are difficult to be identified with hematoxylin and eosin stain. C-cells are positive for calcitonin, chromogranin, and synaptophysin.
- The thyroid follicular cells utilize exogenous iodine for the synthesis of thyroxine (T4) and triiodothyronine (T3). Thyroglobulin is synthesized and stored as colloid. Hydrolysis of thyroglobulin leads to the release of T3 and T4 as colloid from the follicular lumen is endocytosed. This process is regulated by thyroid stimulating hormone (TSH). T4 is resorbed within the thyroid cells and then transferred to the plasma, which is also regulated by TSH. The breakdown of thyroglobulin and release of T3 and T4 are inhibited by various chemicals including iodine, which inhibits the stimulation of thyroid adenylate cyclase by thyroid stimulating hormone. C-cells produce calcitonin, which lowers serum calcium by acting on bone, kidney, and the gastrointestinal tract.

Pigment, Crystals, and Teflon

- Iron pigment can be seen in the thyroid when there has been traumatic hemorrhage and in disorders of iron metabolism. Minocycline chronically ingested can result in the classic “black thyroid.” Minocycline pigment is dark brown/black and located in the apical portion of the follicular cells and in the colloid. Birefringent calcium oxylate crystals are seen in benign and malignant thyroid parenchyma, a helpful feature in distinguishing thyroid from parathyroid gland. Teflon paste injected for vocal cord paralysis can be found in thyroid tissue associated with granulomatous inflammation.

Aplasia and Hypoplasia of Thyroid

- Thyroid aplasia and hypoplasia are the most common causes of congenital hypothyroidism. Patients with Di George syndrome, which is associated with arrested development of the parathyroid and thymus glands associated with the third and fourth bronchial pouches, also have arrested C-cell development.

Heterotopic and Ectopic Thyroid

Clinical

- Heterotopic thyroid tissue is a normal thyroid tissue found along the course of thyroglossal duct (from foramen cecum in posterior tongue down along anterior midline to below cricoid cartilage). Rarely, thyroid tissue may be identified in ectopic sites such as the mediastinum, pericardium, chest wall, vagina, and porta hepatis. Up to 10% of population may have heterotopic thyroid tissue, although it is usually subclinical due to small size. Clinically, it can present as a nodule in the midline neck or base of tongue (most common location). Patients with heterotopic thyroid (especially those with lingual thyroid) may lack a normal thyroid gland. Heterotopic tissue can give rise to thyroid malignancies such as papillary carcinoma. Additionally, the presence of normal-appearing thyroid tissue in lymph nodes most likely represents metastatic papillary thyroid carcinoma to lymph nodes, especially if the lymph nodes are located lateral to the jugular vein rather than heterotopic or ectopic thyroid tissue.

Macroscopic (Fig. 20.1)

- Heterotopic and ectopic thyroid tissue may be encapsulated and resemble normal thyroid tissue.

Microscopic (Fig. 20.2)

- Heterotopic and ectopic thyroid tissue is a histologically normal thyroid tissue, but can manifest pathologic processes that affect the thyroid gland (hyperplasia, neoplasia, inflammation, etc.). Individual follicles may proliferate between adjacent structures (such as muscle) simulating invasion.

Differential Diagnosis

- Metastatic thyroid carcinoma
  - Follicular carcinoma or follicular variant of papillary carcinoma may resemble normal thyroid tissue; thus, careful examination for solid areas, necrosis, mitoses, anaplasia, true invasion, or cytologic features of papillary thyroid carcinoma is needed to rule out a metastasis.

Fig. 20.1. Lingual thyroid: Depression at the site of excision of lingual thyroid.
Parasitic Nodule

Clinical
- A parasitic nodule is a thyroid nodule in the neck that is anatomically separate from the main thyroid gland. The background thyroid gland is often a multinodular goiter. The parasitic nodule probably results from a colloid or hyperplastic nodule located outside of the thyroid gland, which becomes enlarged and migrates laterally in the neck.

Macroscopic
- Parasitic nodules range in size from 1 to 4 cm and may be connected to the thyroid gland by a thin strand of fibrous vascular tissue or it may be completely separate and blood supply from the surrounding tissues.

Microscopic
- The histologic appearance is similar to normal thyroid tissue with hyperplastic or colloid-filled follicles.

Differential Diagnosis
- Metastatic thyroid carcinoma
  - The presence of many lymphoid cells in a patient with Hashimoto thyroiditis and a parasitic or sequestered nodule may lead to a mistaken diagnosis of metastatic carcinoma to a lymph node. Thus, careful determination of the exact location of the tissue is important as well as the histologic features.

Thyroglossal Duct Cyst

Clinical
- Thyroglossal duct cyst is a cystic dilation of remnant of thyroglossal duct, found along course of thyroglossal duct (from posterior tongue down along the anterior midline to below cricoid cartilage). The duct may run anterior to, within, or posterior to the hyoid bone.
- Thyroglossal duct cysts are usually present in childhood with a midline nodule that may be tender and can be associated with the sinus tract. Fistulas may develop secondary to infection and may open into the pharynx or skin.

Macroscopic
- Thyroglossal duct cyst is filled with mucin and measures up to 3 cm in diameter. Normal thyroid tissue may be seen in the wall of the cyst.

Microscopic (Figs. 20.3 and 20.4)
- Thyroglossal ducts cysts are usually lined by pseudostratified ciliated or squamous epithelium. The epithelial lining may not be identified if inflammation is prominent. The surrounding stroma shows thyroid follicles and inflammation.

Differential Diagnosis
- Heterotopic thyroid
  - Heterotopic thyroid shows only thyroid tissue, with no cyst or duct lining.
- Branchial cleft cyst
Located in the anterolateral neck, branchial cleft cysts lack the classic midline location of thyroglossal duct cysts. Branchial cleft cysts are lined by mixed squamous and respiratory epithelium and are associated with lymphoid follicles, but no thyroid tissue is seen.

Thyroid neoplasm with cystic degeneration

Follicular adenoma, adenomatous goiter, or carcinoma may show cystic change. Thus, careful examination of the cyst wall and surrounding tissue is important.

Acute Thyroiditis

Clinical

Acute thyroiditis is usually caused by bacteria, although fungi and viruses have also been implicated. Usually, the thyroid is secondarily involved by a systemic infection or local infection in the neck.

Patients often present with chills, fever, and malaise and an enlarged and painful thyroid. Gram-positive organisms such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus epidermidis*, and *Streptococcus pneumoniae* are most common, but Gram-negative bacilli can also be isolated.

Macroscopic

The thyroid may be enlarged, with areas of necrosis and abscesses.

Microscopic

Acute thyroiditis is characterized by acute inflammation of the thyroid gland with neutrophils and microabscess formation as well as foci of necrosis. Special stains for bacteria and fungal organisms can help identify the organism.

Differential Diagnosis

Other types of thyroiditis (granulomatous or lymphocytic)

In other types of thyroiditis, predominant inflammatory cells are either histiocytes or lymphocytes (neutrophils, if present, usually represent minority) and are not associated with other acute infections or trauma.

Trauma and ischemic necrosis

Although trauma and ischemic necrosis may present with pain, histologically these entities lack the marked acute inflammation and abscess formation seen in acute infectious thyroiditis.

Granulomatous Thyroiditis

Clinical

Granulomatous inflammation occurs in the thyroid in a variety of conditions including infection, sarcoidosis, foreign body reaction, reaction to hemorrhage, among others.

Granulomatous thyroiditis includes nonsuppurative thyroiditis, subacute thyroiditis, and De Quervian thyroiditis.

Women are more commonly affected than men.

Granulomatous thyroiditis is usually associated with pain and systemic symptoms such as fever, malaise, and weakness. The clinical course of granulomatous thyroiditis has been divided into hyperthyroid phase, hypothyroid phase, and recovery phase.

The etiology is unknown, but some cases of granulomatous thyroiditis are thought to be caused by a viral infection, either systemic or an infection of the thyroid itself. Many patients have recently had an upper respiratory infection, and epidemiology studies have shown association with numerous viruses (mumps, Coxsackie, adenovirus, influenza, Epstein Barr, measles, mononucleosis, among others).

The overwhelming majority of patients recover in a few months. Mild cases are treated with aspirin, while prednisone is used in severe cases.

Macroscopic (Fig. 20.5)

The thyroid is enlarged (usually asymmetrical) up to twice normal size. The cut surface shows areas of irregular firm tan tissue among more normal-appearing thyroid tissue.

Microscopic (Fig. 20.6)

Granulomatous thyroiditis is characterized by patchy uneven involvement of the thyroid by neutrophils and microabscesses early to mixed lymphohistiocytic inflammation and vague, noncaseating granulomata with foreign body-type giant cells centered on and destroying follicles and engulfing free colloid. Patchy areas of fibrosis and regenerating follicles may be seen later in the disease.

Differential Diagnosis

Autoimmune thyroiditis

Autoimmune thyroiditis shows significantly less inflammation, which is predominantly lymphocytic with germinal centers. There is no gland destruction; rather, follicles show atrophy with Hürthle cell change.

Acute thyroiditis

Acute thyroiditis is usually associated with infections (bacterial or fungal) or local trauma. Inflammation is predominantly neutrophilic rather than granulomatous.
Histologically, patchy, multifocal mixed lymphocytic and histiocytic foci of inflammation are identified involving isolated and widely distant follicles, in an otherwise histologically normal gland.

**Reidel Fibrous Thyroiditis**

**Clinical**
- Riedel fibrous thyroiditis is a rare, idiopathic inflammatory process manifested by extensive fibrosis of the thyroid gland, extending beyond the gland into the surrounding tissue and usually involving the cervical musculature.
- Fibrous thyroiditis may be related to fibrosing mediastinitis and retroperitoneal fibrosis (idiopathic fibrosclerosis).
- Patients tend to be adult or elderly (average age = 50 years), with slight female predilection. Patients present with painless, poorly defined, thyroid enlargement that is often firm to rock hard.

**Macroscopic (Fig. 20.7)**
- The thyroid gland is enlarged and hard with white fibrous tissue replacing parenchyma and extending into surrounding tissue, obliterating normal anatomic boundaries and extending into adjacent muscles, nerves, and vessels, making excision difficult or impossible.

**Microscopic (Fig. 20.8)**
- The thyroid shows extensive fibrosis, infiltrating beyond the thyroid into the muscle and other tissue, with keloid-like hyalinized collagen. Areas of more normal uninvolved thyroid are seen. There is a patchy lymphoid and plasmacytic infiltrate.
- Involved vessels may show mural inflammation and occlusive phlebitis.
- Giant cells are not prominent, which helps to differentiate Reidel thyroiditis from granulomatous thyroiditis, although

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**Tuberculosis or mycosis**
- Tuberculosis or fungal infections of the thyroid are extremely rare, generally occurring in patients with disseminated systemic involvement. Histologically, the thyroid shows necrotizing granulomas.

**Sarcoidosis**
- Sarcoidosis involving the thyroid occurs in patients with systemic sarcoidosis. The granulomas are interstitial and do not result in follicular destruction.

**Palpation thyroiditis**
- Palpation thyroiditis is an incidental finding as a result of vigorous palpation of or minor trauma to the thyroid.

---

**Fig. 20.5.** Granulomatous thyroiditis: Localized involvement of the right upper lobe by a demarcated tan-yellow inflammatory mass.

**Fig. 20.6.** Granulomatous thyroiditis: Normal thyroid parenchyma has largely been replaced by fibrosis and an inflammatory mass, including multinucleated giant cells. Thyroid follicles are in various stages of destruction.

**Fig. 20.7.** Reidel fibrous thyroiditis: Ragged external aspect of 230 g thyroid gland. Portion of the strap muscles are inextricably attached to the left lobe.
granulomatous thyroiditis lacks that extensive fibrosis seen in Reidel thyroiditis

**Differential Diagnosis**

- **Fibrosing Hashimoto thyroiditis**
  - Patients with the fibrous variant of Hashimoto thyroiditis are hypothyroid (although Riedel thyroiditis can also be associated with hypothyroidism), have high antibody titers, and lack pressure symptoms. The thyroid gland in fibrosing Hashimoto thyroiditis is also involved by fibrosis, but the capsule remains intact and may be separated from adjacent structures. Microscopically, fibrosis appears more typical in fibrosing Hashimoto thyroiditis, rather than the keloid-like collagen seen in Riedel fibrous thyroiditis. Occlusive phlebitis and vasculitis may be seen in Riedel thyroiditis, but not in the fibrous variant of Hashimoto thyroiditis

- **Granulomatous thyroiditis**
  - Giant cells are not prominent in Riedel thyroiditis, which helps to differentiate Riedel thyroiditis from granulomatous thyroiditis. Granulomatous thyroiditis also lacks the extensive fibrosis seen in Riedel thyroiditis

**Lymphocytic Thyroiditis**

**Clinical**

- Lymphocytic thyroiditis is an autoimmune thyroiditis caused by autoantibodies directed against thyroglobulin and other follicular cell antigens

- Lymphocytic thyroiditis is usually seen in children and adults and is more common in women (F:M = 2:1). Patients present with asymptomatic goiter and may have transient hyperthyroidism. The process usually resolves within 1 year

**Macroscopic**

- The thyroid shows mild to moderate enlargement and has a slightly nodular appearance

**Microscopic** *(Figs. 20.9 and 20.10)*

- The thyroid shows scattered interstitial lymphoid follicles with germinal centers. The follicles typically show minimal reaction to inflammation, but there may be some mild atrophy or Hürthle cell change

**Differential Diagnosis**

- **Hashimoto thyroiditis**
  - Hashimoto thyroiditis has larger, more numerous lymphoid follicles and scattered plasma cells and histiocytes than lymphocytic thyroiditis. Hürthle cell change is present in Hashimoto thyroiditis

- **Graves disease**
  - Graves disease is associated with hyperthyroidism. The thyroid shows diffuse follicular hyperplasia often with a prominent papillary architecture

Fig. 20.8. Riedel fibrous thyroiditis. Hyalinized fibrous proliferation has penetrated through the thyroid capsule and surrounds islands of metaplastic squamous epithelium. There is a lymphocytic infiltrate focally.

Fig. 20.9. Lymphocytic thyroiditis (painless thyroiditis): Vim-Silvermann needle biopsy of a patient with transient hyperthyroidism. There is a moderately heavy lymphocytic infiltrate involving variable-sized thyroid follicles.

Fig. 20.10. Lymphocytic thyroiditis (painless thyroiditis): Focal heavy lymphocytic infiltrate with follicles showing degenerative changes characterized by swelling of lining follicular cells and inflammatory infiltration.
**Hashimoto Thyroiditis**

**Clinical**
- Hashimoto thyroiditis is an autoimmune thyroiditis characterized by a goiter and circulating antithyroglobulin and antithyroid peroxidase (antimicrosomal) antibodies.
- Classically, Hashimoto thyroiditis occurs in young to middle-aged females (30–50 years old; F:M = 10:1). Hashimoto thyroiditis is the most common thyroid disease in children and adolescents. Different HLA haplotypes have been associated with Hashimoto disease. Hashimoto thyroiditis is associated with other autoimmune diseases. Hashimoto thyroiditis may be associated with autoimmune disease of adrenals (Addison disease), pancreas (diabetes), or stomach (pernicious anemia). Individuals with Down syndrome have an increased susceptibility to autoimmune thyroid diseases, including Hashimoto thyroiditis.
- Patients present with diffuse firm goiter, tenderness, and hyperthyroidism. As the disease progresses, thyroid function decreases, eventually resulting in hypothyroidism.
- There is an increased risk of lymphoma, leukemia, and thyroid carcinoma.

**Macroscopic**
- The thyroid gland shows diffuse, firm enlargement. The cut surface may show areas of fibrosis and pale tan color due to the chronic inflammatory infiltrate, unlike the beefy red diffuse appearance of the thyroid in Graves disease. Increasing fibrosis is noted with increasing age.

**Microscopic (Figs. 20.11 and 20.12)**
- The thyroid shows marked interstitial lymphocytic inflammation with prominent lymphoid follicles with germinal centers. The thyroid follicles are small and atrophic lined by oxyphilic epithelium (Hürthle cells). Interstitial fibrosis may accentuate lobular architecture. Regenerative hyperplasia and squamous metaplasia may be seen.

**Variants**
- Fibrosing Hashimoto thyroiditis
  - Approximately 10% of Hashimoto thyroiditis shows prominent fibrosis, which is usually seen in elderly patients. The thyroid shows marked enlargement with some adhesion of gland to surrounding tissue (although surgical planes are readily identifiable). Histologically extensive fibrosis, follicular atrophy with Hürthle cell change, squamous metaplasia and lymphocytes and plasma cells are seen. This variant may be confused with Riedel thyroiditis as well as carcinoma due to its adherence to adjacent structures. The parenchyma of Hashimoto thyroiditis retains its normal lobular architecture and lacks cytologic features of malignancy.
  - The prominent lymphoplasmacytic infiltrate in Hashimoto thyroiditis can be mistaken for malignant lymphoma. Because thyroid lymphomas usually arise in the setting of Hashimoto thyroiditis, a high index of suspicion is needed when examining thyroid tissues with prominent lymphoid infiltrates.

**Differential Diagnosis**
- Lymphocytic thyroiditis
  - Lymphocytic thyroiditis shows milder inflammation, with scattered lymphoid follicles and little or no reactive changes in thyroid follicles.
- Graves disease
  - The follicles in Graves disease appear hyperplastic, rather than atrophic.

**Postpartum Thyroiditis**
- Postpartum thyroiditis is an autoimmune disorder, associated with microsomal antibodies, which affects women in the first postpartum year. Postpartum thyroiditis has an early thyrotoxic phase and a longer hypothyroid phase. Histologically, postpartum thyroiditis is shown by focal or diffuse chronic thyroiditis and resembles spontaneous silent thyroiditis. The hypothyroid phase is characterized by follicular disruption and hyperplasia while focal lymphocytic thyroiditis is seen in the recovery phase.
Focal Lymphocytic Thyroiditis

♦ Focal lymphocytic thyroiditis (nonspecific thyroiditis, focal autoimmune thyroiditis) is thought to be an incidental finding, which usually affects elderly, is more common in women than in men, and is relatively common with autopsy studies showing 20% of thyroids are involved. The thyroid shows dense lymphoid aggregates with or without germinal centers.

Graves Disease

Clinical

♦ Graves disease (diffuse hyperplasia) is an autoimmune thyroiditis caused by autoantibodies directed against thyroid stimulating hormone receptors, resulting in chronic follicular stimulation and hyperthyroidism (diffuse toxic goiter).

♦ Graves disease is most commonly seen in young females (20–40 years old; F:M = 4:1) and may occur in children. In the United States, Graves disease affects about one of every 2,000 people.

♦ Patients present with diffuse goiter and hyperthyroidism. Patients often have a family history of autoimmune diseases. Graves disease is diagnosed clinically by physical examination and laboratory testing including elevated serum thyroxine with low TSH, and high radioactive iodine uptake.

♦ Untreated, Graves disease can cause severe thyrotoxicosis, osteoporosis, catabolism of muscle and bone with myopathy, among others complications.

Macroscopic (Fig. 20.13)

♦ The thyroid shows mild to moderate diffuse enlargement, has soft consistency and pink tan color.

Microscopic (Figs. 20.14–20.16)

♦ The thyroid shows markedly hyperplastic follicles lined by active tall columnar cells showing clear, sometimes

Fig. 20.13. Graves disease: Enlarged thyroid (94 g) with a glistering, finely nodular cut surface.

Fig. 20.14. Graves disease: Irregularly shaped follicles are partially filled with pale colloid.

Fig. 20.15. Graves disease: Follicles show multiple papillary infoldings and some scalloping of the colloid.

Fig. 20.16. Graves disease: Cubical and low columnar eosinophilic epithelium lines follicles, one of which has a papillary infolding.
vacuolated, cytoplasm. Colloid appears pale and depleted, with scalloped edges at the epithelial border. Epithelial hyperplasia resulting in papillae with fibrovascular cores, resembling papillary carcinoma is characteristically seen.

- Interstitial lymphoid aggregates with germinal centers may be present
- The classic appearance is usually altered by preoperative medication. Iodine therapy can greatly diminish hyperplasia, resulting in an almost normal-appearing gland with involution of the epithelium with cuboidal rather than columnar cells, increased colloid, and decreased vascularity while propylthiouracil and methimazole therapy are associated with hyperplastic changes.

**Differential Diagnosis**

- Papillary thyroid carcinoma
  - Papillary thyroid carcinoma generally presents as a mass, rather than a diffuse process. Histologically, classic cytologic features of papillary thyroid carcinoma (ground glass nuclei, nuclear grooves, and nuclear pseudo inclusions) are identified.
  - In difficult cases of Graves disease with papillary hyperplasia, p27 protein and HBME-1 may be used to separate these two lesions. p27 shows higher expression in Graves disease compared with papillary thyroid carcinoma.

- Lymphocytic thyroiditis
  - Lymphocytic thyroiditis usually affects young patients who are euthyroid. Thyroid follicles appear normal or show only mild atrophy when compared with the hyperplastic follicles classic of Graves disease.

- Hashimoto thyroiditis
  - Hashimoto thyroiditis show atrophy and Hürthle cell change, not hyperplasia.

- Toxic nodular goiters
  - Toxic nodular goiters can also be associated with hyperthyroidism, but appear more multinodular than the diffuse appearance of the thyroid in Graves disease. Additionally, histologic involvement of the thyroid is focal in toxic nodular goiters while it is diffuse in Graves disease.

**Nontoxic Simple and Multinodular Goiters**

**Clinical**

- Goiter means enlarged thyroid gland. Simple nontoxic goiters can be sporadic or endemic. Sporadic nontoxic goiter is the most common nontoxic goiter. Sporadic goiters are identified in approximately 5% of the population, are more common in women, and are uncommon in children. The cause of sporadic goiters is generally unknown, but they can be associated with some medications and may have a hereditary component. When the thyroid cannot produce sufficient thyroid hormone, the gland enlarges to overcome this deficiency. Endemic goiters are seen in areas of iodine deficiency and have become relatively uncommon due to iodized table salt.

- Most patients are euthyroid, presenting with symptoms of simple or multinodular thyroid enlargement, which may be generalized or have dominant nodule. Goiters may cause obstructive symptoms due to tracheal or esophageal compression and voice change due to laryngeal nerve compression. Goiters are usually slow-growing and painless. A sudden increase in growth, a new nodule, or a dominant nodule in a multinodular goiter are concerning for malignancy. Goiters are treated with thyroxine, radioactive iodine, and surgery and can recur.

**Macroscopic (Fig. 20.17)**

- The thyroid gland is enlarged in both simple and multinodular goiters. Simple goiters are diffusely enlarged, while multinodular goiters show multiple nodules grossly. The normal thyroid gland weighs 15–25 g, while goiterous thyroid glands can weigh over a hundred grams.

**Microscopic (Fig. 20.18)**

- The histologic features of goiters can be varied. Goiters are generally composed of a mixture of small follicles with cuboid...
Follicular neoplasms

Macroscopic

Clinical

Toxic multinodular goiters are composed of a mixture of hypercellular nodules with tall columnar cells, papillary hyperplasia, and inactive appearing nodules with flat epithelium

Differential Diagnosis

Endemic and sporadic multinodular goiters show similar histologic features

Multinodular goiters show many nodules of different sizes, some encapsulated, compress the adjacent thyroid parenchyma. An individual nodule, particularly a dominant nodule, in a multinodular goiter can be difficult to be distinguished from a follicular adenoma

Degenerative changes with hemorrhage, fibrosis, and calcification are common

Microscopic

Dyshormonogenetic Goiter

Clinical

Dyshormonogenetic goiters are usually due to an autosomal recessive genetic defect in the synthesis of thyroid hormone. Although most dyshormonogenetic goiters develop in childhood, they can be identified over a wide age range. Patients present with hypothyroidism, goiter, or growth deficiencies. Patients with congenital goiter and congenital sensorineural deafness have a defect in the Pendred syndrome gene, 7q22-31.1, which encodes pendrin, an iodide/chloride transporter

Macroscopic

Dyshormonogenetic goiters are large and multinodular

Microscopic

The nodules are diffusely hypercellular and show an irregular growth pattern. The follicular cells show nuclear atypia and mitotic activity and can be confused with malignancy. Thyroid carcinomas, particularly follicular, can occur in these goiters

Toxic Multinodular Goiter

Clinical

Toxic multinodular goiters are multinodular goiters associated with thyrotoxicosis, although these patients lack the ophthalmic changes seen in Graves disease. Multinodular goiters may be present for years, and may insidiously become toxic goiters

Macroscopic

Grossly toxic multinodular goiters appear similar to nontoxic multinodular goiters. Both are enlarged thyroids composed of multiple nodules with fibrosis

Microscopic

Macroscopic

Papillary Thyroid Carcinoma

Clinical

Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma, accounting for approximately 80% of thyroid carcinomas. They occur in adults and children, with females being affected more commonly than males. Rare familial PTC can occur

A variety of thyroid disorders including Graves, Hashimoto thyroiditis, and hyperplastic nodules have been identified with PTC. PTCs are associated with a history of radiation exposure, and radiation associated tumors have been associated with aggressive behavior and solid growth pattern

Papillary thyroid carcinomas are often irregular or well demarcated masses on ultrasound and cold nodules on radioactive iodine scan

The prognosis of PTC is generally excellent, with overall survival greater than 90%. Poor prognostic factors include increased age (>40 years), male sex, large tumor size, multicentricity, vascular invasion, extrathyroid extension, distant metastases, and dedifferentiation to poorly differentiated and anaplastic thyroid carcinoma. Variants of PTC with more aggressive behavior include tall cell, columnar cell, and solid variant

Papillary thyroid carcinomas are often treated by complete thyroidectomy, ipsilateral lymph node dissection, and radioactive iodine can be used to ablate any remaining tumor

Macroscopic

Papillary thyroid carcinomas are variably sized, from microscopic to >10 cm, usually 2–3 cm, solid, white, infiltrating masses, often with a granular cut surface and calcifications. These tumors may be single or multiple and may undergo cystic change

Microscopic (Figs. 20.19 and 20.20)

Papillary thyroid carcinomas are composed of complex papillae with single layer or stratified epithelial cells supported by branching fibrovascular cores lined by follicular cells with characteristic cytomorphic features. Classic cases usually show a predominance of papillary structures, although this feature can be extremely variable. Foci of more follicular areas and solid areas as well as squamous metaplasia can be seen

Diagnostic nuclear features include nuclear enlargement, nuclear irregularity, ground glass nuclei (large optically clear “Orphan Annie” nuclei that tend to overlap), nuclear grooves
Psammoma bodies (laminated basophilic bodies) occur in 50% of cases and are more common in tumors with prominent papillary growth. The colloid in PTC is often darker than that of the surrounding normal thyroid. The stroma is often abundant, fibrous, and sclerotic. A lymphocytic infiltrate can be seen at the periphery of the tumor lobules. Cystic change is common. Mitotic figures and necrosis are uncommon. A significant number of cases (25–75% depending on sampling) show multiple tumor foci.

Immunohistochemistry

- Papillary thyroid carcinomas are positive for thyroglobulin, thyroid transcription factor (TTF-1), and keratin (see Table 20.1). Papillary thyroid carcinomas are negative for chromogranin, synaptophysin, and calcitonin. Immunohistochemical markers that may be helpful confirming a diagnosis of PTC include HMBE-1, galectin-3, cytokeratin 19, and CITED-1.

**Molecular Genetics**

- BRAF mutations and RET/PTC rearrangements are alternative events in the pathogenesis of PTC.
- BRAF mutations, especially BRAF(V600E), is detected in 36–69% of PTC. BRAF mutations are frequent in PTC with papillary or mixed papillary-follicular growth pattern, Warthin-like PTC, micropapillary PTC, and oncocytic/oxyphilic (Hürthle cell) variant of PTC. BRAF mutations are rarely detected in pediatric or radiation associated PTC. BRAF mutations are also present in poorly differentiated and anaplastic carcinomas arising from PTC.
- RET/PTC rearrangement is identified in approximately 20–30% of PTC, although the prevalence varies among geographical sites and tumor subtypes. This rearrangement is particularly common in radiation associated PTC. RET/PTC1 and RET/PTC3 account for greater than 90% of the rearrangements. RET/PTC1 is more common in papillary microcarcinomas, tumors with classic papillary growth, and a more benign clinical course, while RET/PTC3 is more common in the solid variant of PTC and aggressive behavior.

**Variants**

- **Papillary microcarcinoma**
  - Papillary microcarcinoma is defined as a PTC measuring 1 cm or less. These tumors are usually indolent, incidental findings in thyroids removed for benign clinical nodules or thyroditis. Autopsy and surgical studies show that approximately 8% of thyroids when serially sectioned will have a papillary microcarcinoma.
  - The treatment for papillary microcarcinoma has been controversial. Papillary microcarcinomas presenting as a clinical mass or a lymph node metastasis are treated as a clinical cancer. In up to 15–20% of papillary microcarcinomas, another focus is the contralateral lobe, and that long-term recurrent disease may reach 20% in the absence of complete resection. Despite their small size, 5% of these microcarcinomas may be associated with invasion of the capsule or distant metastases. When papillary microcarcinomas present as a clinically occult incidental finding, the behavior appears more indolent than those presenting clinically, and some suggest a conservative approach to management.

- **Follicular variant of PTC**
  - Follicular variant of PTC (FVPTC) is the most common variant of PTC and is also the most difficult type to diagnose. Encapsulated tumors can be particularly problematic if the tumor shows only borderline features for PTC. These tumors can show a microfollicular, macrofollicular, or diffuse growth pattern. Differentiating FVPTC from the follicular neoplasms can be extremely difficult. Cytologic features classic of PTC may only be focally noted in FVPTC. Important diagnostic features of FVPTC are nuclear pseudoinclusions (cytoplasmic invaginations into the nucleus), abundant nuclear grooves, and ground glass nuclei. Immunohistochemical
studies such as HBME-1, CK19, galectin, and CITED are helpful in separating some cases of FVPTC from follicular adenoma. FVPTC behaves similarly to conventional PTC.

- Tall cell variant of PTC
  - The tall cell variant of PTC is more common in the elderly and in males. These tumors are usually large at diagnosis. Histologically, prominent papillary structures are lined by cells that are least twice as tall as they are wide. The tall cells have basally located nuclei and abundant eosinophilic cytoplasm. The tall cell variant of PTC is associated with extrathyroidal disease, vascular invasion, recurrence, and metastases. These are aggressive tumors with shorter disease-free survival than conventional PTC, and have a fatality rate of up to 25%.

- Columnar variant of PTC
  - The columnar variant of PTC is an uncommon, aggressive variant of PTC that occurs over a wide age range, can metastasize widely, and usually does not respond to radioactive iodine or chemotherapy. The columnar variant has a prominent papillary architecture and elongated cells with nuclear stratification and scant cytoplasm.

- Solid variant of PTC
  - The solid variant of PTC is uncommon, comprising only 2–3% of PTC, is more common in children, and may be associated with radiation exposure. This variant has a less favorable prognosis than classic PTC.

- Diffuse sclerosing variant of PTC
  - The diffuse sclerosing variant of PTC is more common in women and younger patients. This variant is characterized by diffuse thyroid involvement, intrathyroid lymphatic spread, squamous metaplasia, prominent psammoma bodies, fibrosis, and a lymphocytic infiltrate. This variant shows frequent cervical lymph node as well as lung metastases. Some studies have found decreased survival while others have shown similar to survival to classic PTC.

- Oxyphilic (oncocytic/Hürthle cell variant of PTC)
  - The oxyphilic (oncocytic/Hürthle cell) variant of PTC is uncommon. These tumors often show a papillary architecture, have oxyphilic cytoplasm, and nuclear features classic of PTC. This variant may behave similarly to or more aggressively than classic PTC, depending on the study.

- Warthin-like variant of PTC
  - The Warthin-like variant of PTC resembles a Warthin tumor of the salivary gland with oxyphilic cells and lymphocytic stroma. However, the cytologic features are classic of PTC, and these tumors behave similarly to classic PTC.

- Cribriform-morular variant of PTC
  - The cribriform-morular variant of PTC can occur sporadically, but often occurs in the setting of familial adenomatous polyposis with germ line APC gene mutations. These tumors are often multicentric and are more common in women. These tumors show cribriform, solid/trabeucular, and morular growth and cytologic features classic of PTC. These tumors behave similarly to conventional PTC.

- Clear cell variant of PTC
  - The clear cell variant of PTC is uncommon and behaves similar to conventional PTC. This variant must be differentiated from other clear cell tumors such as metastatic renal cell carcinoma.

- Papillary thyroid carcinoma with nodular fasciitis-like stroma

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### Table 20.1. Immunohistochemical Profile of Thyroid Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Thyroglobulin</th>
<th>TTF</th>
<th>Keratin</th>
<th>Calcitonin</th>
<th>Chromogranin</th>
<th>Synaptophysin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary thyroid carcinoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Follicular and Hürthle cell thyroid tumors</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Poorly differentiated thyroid carcinoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anaplastic thyroid carcinoma</td>
<td>Focal</td>
<td>Focal</td>
<td>Focal</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>–</td>
<td>+</td>
<td>+ (CAM 5.2)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*TTF: thyroid transcription factor*
Rarely, PTC shows prominent nodular fasciitis-like stroma that can be mistaken for a mesenchymal tumor or an anaplastic thyroid carcinoma. Small tubules and nests of epithelioid cells with cytologic features characteristic of PTC are noted in a nodular-fasciitis-like stroma.

- Papillary thyroid carcinoma with lipomatous stroma
- Papillary thyroid carcinoma can show a lipomatous stroma. Lipomatous stroma is not specific for PTC as it can also be seen in adenomatous nodules, follicular neoplasms, goiters, and lymphocytic thyroiditis

**Differential Diagnosis**

- Graves disease
  - Graves disease can show papillary architectural features, but it lacks typical nuclear features such as nuclear clearing, large nuclei with irregular nuclear membranes, nuclear clearing (“Orphan Annie” nuclei), nuclear grooves, and intranuclear holes are helpful in separating PTC from Graves

- Hyalinizing trabecular tumor (Figs. 20.21 and 20.22)

  - The nuclei in hyalinizing trabecular tumors are similar to those of PTC, and occasional psamomma bodies can be seen in hyalinizing trabecular tumors. However, hyalinizing trabecular tumors often resemble neuroendocrine neoplasm (paraganglioma or medullary thyroid carcinoma). Hyalinizing trabecular tumors are characterized by trabecular growth pattern with prominent intratrabecular hyaline material. Hyalinizing trabecular tumors show a characteristic cytoplasmic staining pattern for MIB1 (Ki-67), which can also be helpful in their diagnosis

- Follicular carcinoma
  - Follicular thyroid carcinomas may resemble PTC, particularly FVPTC. Follicular thyroid carcinomas do not show papillary architecture or classic cytologic features (nuclear grooves, intranuclear cytoplasmic inclusions) of PTC

- Follicular adenoma
  - Follicular adenomas may resemble PTC, particularly FVPTC. Follicular adenomas do not show papillary architecture, invasive growth, or classic cytologic features (nuclear grooves, intranuclear cytoplasmic inclusions) of PTC. Cytologic features classic of PTC may only be focally noted in follicular variant of PTC often at the peripheral aspect of the tumor. Important features to diagnose follicular variant of PTC are nuclear pseudoinclusions (cytoplasmic invaginations into the nucleus), abundant nuclear grooves, and ground glass nuclei. Immunoperoxidase studies, including HBME-1, galectin-3, and cytokeratin 19 can also be helpful in difficult cases as PTC are usually positive

- Hürthle cell tumors
  - The Warthin-like variant and oxyphilic variant of PTC can be mistaken for benign Hürthle cell tumors. Cytologic features classic of PTC are helpful in separating the Warthin-like variant of PTC from Hürthle cell tumors. The prominent lymphoplasmacytic infiltrate seen in Warthin-like variant of PTC is a low power clue to the diagnosis
Hyalinizing Trabecular Tumor

Clinical

- Hyalinizing trabecular tumors are unique can mimic PTC and medullary thyroid carcinoma. The biologic potential has been controversial, but the overwhelming majority of these tumors behave in an indolent fashion. They should probably only be treated as a malignancy when there is obvious capsular or vascular invasion or metastasis.

Macroscopic

- Hyalinizing trabecular tumors are circumscribed, yellow-tan, encapsulated nodules that measuring 0.3–4 cm in diameter.

Microscopic (Figs. 20.21 and 20.22)

- Hyalinizing trabecular tumors are circumscribed or encapsulated solid tumors that show a trabecular growth pattern with prominent extracellular eosinophilic hyaline fibrosis that is reminiscent of amyloid but negative for Congo red.
- The trabeculae and nests of cells are composed of polygonal and elongated cells with oval nuclei with perinucleolar vacuoles, nuclear inclusions, nuclear grooves, and fine granular cytoplasm. The prominent intranuclear cytoplasmic inclusions can cause confusion with PTC.
- Cytoplasmic yellow bodies are frequently noted in hyalinizing trabecular tumors, but these are not specific as they can be seen in other tumors.

Immunohistochemistry

- Hyalinizing trabecular tumors are positive for thyroglobulin and TTF-1 and negative for calcitonin, chromogranin, and CEA. These tumors also show characteristic cytoplasmic and cell membrane staining for MIB1 (Ki-67).
- Galectin-3 shows variable staining. HBME-1, a marker that is usually positive in PTC is negative in hyalinizing trabecular tumors.

Molecular Genetics

- Ret protooncogene rearrangements are a common finding in PTC, and have been detected by RT-PCR and immunohistochemistry in some cases. However, some of the cases also harbored PTC, thus this finding is difficult to interpret.
- BRAF mutations are generally not detected in hyalinizing trabecular tumors.

Differential Diagnosis

- Medullary thyroid carcinoma.
  - The trabecular growth pattern, elongated cells, and hyalinization, which are reminiscent of amyloid, are features of hyalinizing trabecular tumor that can be confused with medullary thyroid carcinoma. However, the hyaline material, unlike amyloid, is negative for Congo red. Cytologically, the nuclear features of hyalinizing trabecular tumors are more similar to PTC rather than the neuroendocrine nuclear features seen in medullary thyroid carcinoma. The immunophenotype is also helpful in differentiating these tumors as hyalinizing trabecular tumors are positive for thyroglobulin and negative for chromogranin, synaptophysin, and calcitonin.
- Papillary thyroid carcinoma.
  - Hyalinizing trabecular tumors show prominent nuclear inclusions, a feature often seen in PTC. However, the nuclear inclusions are much more prominent and numerous in hyalinizing trabecular tumors. Additionally, PTC generally lacks the trabecular growth pattern and prominent stromal hyalinization characteristic of hyalinizing trabecular tumors. HBME-1 is generally positive in PTC and negative in hyalinizing trabecular tumors. Hyalinizing trabecular tumors also show characteristic cytoplasmic membrane staining with MIB1 (Ki-67).

Follicular Adenoma

Clinical

- Follicular adenomas are benign, encapsulated tumors showing follicular differentiation.
- Follicular adenomas occur in 5–10% of the population, predominantly in adults, and are more common in women. Patients present with a palpable nodule showing little to no I131 uptake or as asymmetrical thyroid enlargement.

Macroscopic

- Follicular adenoma is a single encapsulated nodule, 1–3 cm in size. The cut surface varies from gray-tan to pink and fleshy, depending on cellularity and colloid. Larger adenomas may show hemorrhage, cyst formation, fibrosis, and calcification.

Microscopic

- Follicular adenomas have a complete, usually thin, capsule with compression of surrounding thyroid tissue. No invasion of the capsule or vessels is present.
- A variety of growth patterns may be seen within the nodule including microfollicular, macrofollicular, trabecular, solid, and focal pseudopapillary architecture can be seen occasionally (Figs. 20.23 and 20.24). The growth pattern of cells within nodule classically stands in sharp contrast to appearance of normal thyroid parenchyma outside capsule.
- Many histologic variants of follicular adenoma have been described as follicular adenoma with bizarre nuclei, adenolipomas, adenochondromas, mucinous follicular adenomas, follicular adenomas with clear cell change, follicular adenoma with papillary hyperplasia, and signet ring cell adenomas.
- Atypical follicular adenomas are cellular tumors, which may show nuclear atypia or irregular growth, but lack definitive vascular or capsular invasion. Atypical adenomas usually behave in an indolent fashion.

Immunohistochemistry

- Follicular adenomas are immunoreactive for thyroglobulin, keratin, and TTF-1.
- Follicular adenomas generally do not show prominent staining for HBME-1, CK19, galectin 3, and CITED as is often seen in PTC.
show PAX8 to PPAR gamma (peroxisome proliferator-activated receptor gamma) rearrangements

**Differential Diagnosis**
- Follicular thyroid carcinoma
  - By definition follicular thyroid carcinomas show capsular or vascular invasion, features not seen in follicular adenomas. The capsule in follicular adenomas is usually not as thick as in follicular carcinoma
- Follicular variant of PTC
  - Differentiating follicular adenoma from FVPTC can be extremely difficult as the tumors show architectural similarities. In most cases, FVPTC shows cytologic features classic of PTC, but classic cytologic features of PTC may only be focally noted often near the capsule in FVPTC. Thus careful histologic evaluation is critical to differentiate these entities. Immunohistochemical markers somewhat helpful in this distinction include HBME-1, CK19, and galectin 3
- Adenomatous nodule
  - Adenomatous nodules are usually multiple, but may present as a dominant nodule. Adenomatous nodules are often not completely encapsulated. Prominent secondary hyperplastic papillary changes can be seen
- Hyalinizing trabecular tumor (Figs. 20.21 and 20.22)
  - Hyalinizing trabecular tumors with trabecular growth and prominent hyaline material are very helpful in identification of these tumors. The nuclei are similar to PTC, and numerous intranuclear holes can be seen. Hyalinizing trabecular tumor shows a characteristic cytoplasmic membrane staining pattern for MIB1 (Ki-67)

**Follicular Thyroid Carcinoma**

**Clinical**
- Follicular carcinoma is a malignant epithelial tumor showing follicular differentiation and lacking the diagnostic nuclear features of PTC
- Follicular carcinomas account for 10–15% of thyroid carcinomas, present as a single palpable neck mass, affect females more commonly than males, and occur at an average age of 50 years. A higher incidence of follicular carcinomas is identified in iodine deficient regions. These tumors show little or no 131I uptake
- Unlike PTC, follicular carcinomas show infrequent regional lymph node metastases
- Patients with follicular thyroid carcinomas usually undergo total thyroidectomy. Minimally, invasive follicular carcinomas have an excellent prognosis with a mortality of 5%, while widely invasive carcinomas have a mortality of 50%

**Macroscopic**
- Follicular carcinomas are solid, round to oval tumors, tan to brown in color. These tumors may grossly appear encapsulated or may form a poorly circumscribed mass. The
capsule is often thicker and more irregular than in follicular adenoma

- Widely invasive tumors may show gross capsular or vascular invasion. The cut surface usually appears similar to follicular adenoma (gray-tan to pink and fleshy)

**Microscopic (Figs. 20.25 and 20.26)**

- Histologically, follicular carcinoma can be difficult to distinguish from follicular adenoma. Follicular carcinomas are cellular, show a follicular or solid growth pattern, and lack cytologic features of PTC
- Vascular invasion or capsular invasion is required for the diagnosis of follicular carcinoma. Capsular invasion often shows a mushroom-type of growth through the capsule. This pattern is different from the linear pattern of tumor associated with hemorrhage, inflammation, and young collagen that is seen in fine-needle aspiration sites
- Follicular carcinomas have been classified as minimally and widely invasive based on the amount and type of invasion. Minimally, invasive tumors show focal capsular and/or vascular invasion, while widely invasive carcinomas show many areas of invasion

**Immunohistochemistry**

- Follicular carcinomas are positive for thyroglobulin, TTF-1, and low molecular weight cytokeratin (CAM 5.2) (Table 20.1)

**Molecular Genetics**

- PAX8-PPARgamma translocation t(2;3)(q13;p25) resulting in a fusion oncprotein has been identified in a proportion of follicular carcinomas and occasionally in follicular adenomas. Follicular carcinomas with PAX8-PPAR gamma occur in younger patients with smaller, but overtly invasive, tumors, which are usually positive for galectin-3 and negative for HBME-1
- RAS mutations appear separate from PAX8-PPAR gamma translocations. Follicular carcinomas with RAS mutations are often positive for HBME-1 and negative for galectin-3

**Differential Diagnosis**

- Follicular adenoma
  - Follicular carcinomas shows similar encapsulation and growth patterns as follicular adenomas, but follicular carcinomas by definition show capsular and/or vascular invasion. The capsules of adenomas tend to be thinner than carcinomas
- Papillary carcinoma, follicular variant
  - Follicular variant of PTC may show invasive growth; however, cytologic features of PTC are present. Often, focal papillary differentiation is noted

**Hürthle Cell Adenoma**

**Clinical**

- Hürthle cell adenomas are benign thyroid neoplasms composed exclusively or predominantly of Hürthle cells (oxyphil cells, oncocytes). Women are affected more commonly than men. The mean age at diagnosis is 55 years. These tumors are solitary nodules on ultrasound and show little or no I131 uptake

**Macroscopic (Fig. 20.27)**

- Hürthle cell adenomas are solid tumors, round to oval in shape, encapsulated, and have a brown cut surface typical of oncocytic tumors. Areas of hemorrhage, cyst formation, or calcification may be seen in larger tumors. Infarction can be seen in tumors that have undergone fine-needle aspiration biopsy

**Microscopic (Figs. 20.28 and 20.29)**

- Hürthle cell adenomas are encapsulated and lack capsular or vascular invasion
- The tumors can show a variety of growth patterns including follicles, solid areas, trabecular growth, and papillary growth. They are composed of at least 75% Hürthle cells, which are polygonal cells with abundant granular eosinophilic cytoplasm and large nuclei with prominent nucleoli. Areas of nuclear pleomorphism (“endocrine atypia”) may be identified
Hürthle cell adenomas are positive for thyroglobulin and TTF-1 and are negative for chromogranin, synaptophysin, and calcitonin.

**Differential Diagnosis**

- Hürthle cell carcinoma
  - Hürthle cell adenomas lack capsular and vascular invasion of carcinomas

**Hürthle Cell Carcinoma**

**Clinical**

- Hürthle cell carcinomas malignant neoplasms composed predominantly or exclusively of Hürthle (oncocytic/oxyphilic) cells
- Hürthle cell carcinoma accounts for 2–3% of thyroid carcinomas. Women are more commonly affected than men. The mean age at diagnosis is 55 years. Hürthle cell carcinoma is a well-demarcated nodule on ultrasound and shows little or no I131 uptake
- Hürthle cell carcinomas are slightly more aggressive than follicular carcinomas and have an overall 5-year survival of 50–60%. Hürthle cell carcinomas show extrathyroidal invasion more frequently than follicular carcinomas, and show lymph node metastases more often than follicular carcinomas. However, the most common sites of metastases are lung and bone, followed by regional lymph nodes. Poor prognostic factors include large tumor size and vascular invasion

**Macroscopic**

- Hürthle cell carcinomas are solid, encapsulated, round to oval tumors, with a brown cut surface. They are generally larger than adenomas and have a thicker more irregular capsule. Widely invasive tumors may show gross invasion of the capsule or vessels

**Microscopic**

- Hürthle cell carcinomas are cellular tumors, composed of at least 75% Hürthle cells, and show a follicular, solid, or...
trabecular growth pattern. Hürthle cells are large polygonal cells with round nuclei and nucleoli, abundant granular eosinophilic cytoplasm, and lack cytologic features of papillary thyroid carcinoma

- Vascular or capsular invasion is required for the diagnosis of Hürthle cell carcinoma. Capsular invasion often shows a mushroom-type of growth through the capsule. This pattern is different from the linear pattern of tumor associated with hemorrhage, inflammation, and young collagen that is seen in fine-needle aspiration sites. Hürthle cell carcinomas have been classified as minimally or widely invasive based on the amount and type of invasion. Minimally invasive tumors show focal capsular and/or vascular invasion, while widely invasive follicular carcinomas show many areas of invasion

**Immunohistochemistry**

- Hürthle cell carcinomas are immunoreactive for thyroglobulin, although staining is not as strong as other thyroid follicular neoplasms (Table 20.1). Hürthle cell carcinomas are also positive for TTF-1 and are negative for chromogranin, synaptophysin, and calcitonin

**Molecular Genetics**

- Numeric chromosomal abnormalities including changes in p53 and cyclin D1 and chromosomal gains and have been identified in Hürthle cell carcinomas. These tumors tend to show more chromosomal losses than adenomas. PAX8-PPAR gamma rearrangements and RAS mutations are not frequent in Hürthle cell carcinomas. GRIM-19 point mutations were the first mutation relatively specific to Hürthle cell tumors

**Differential Diagnosis**

- Hürthle cell adenoma
  - Hürthle cell adenomas are usually smaller, have a thinner more regular capsule, and lack diagnostic capsular and vascular invasion of Hürthle cell carcinomas
- Hürthle cell/oxyphilic variant of PTC
  - Hürthle cell carcinomas lack the classic cytologic features of PTC
- Oxyphilic variant of medullary thyroid carcinoma
  - Hürthle cell carcinomas lack the neuroendocrine nuclear features of medullary thyroid carcinoma. In difficult cases, immunohistochemical studies can be helpful as Hürthle cell carcinomas lack staining for chromogranin, synaptophysin, and calcitonin

**Poorly Differentiated Carcinoma**

**Clinical**

- Poorly differentiated carcinomas are follicular cell neoplasms that are in between well-differentiated follicular and papillary carcinomas and undifferentiated or anaplastic carcinomas
- Patients usually present with a large solitary thyroid mass. They often have a history of recent thyroid enlargement or enlargement of a tumor that has been present for a number of years. Patients are usually ≥50 years of age, and women are affected more commonly than men. Poorly differentiated thyroid carcinomas appear to be more common in Italy and Latin America
- Treatment is total thyroidectomy with resection of any involved lymph nodes and radioactive iodine therapy. The prognosis is relatively poor with lymph node and distant metastases being relatively common. The 5-year survival rate is approximately 50%

**Macroscopic**

- Poorly differentiated tumors are large, have a pale, gray-white cut surface with areas of necrosis, and may have a pushing border, extrathyroid extension, and satellite nodules

**Microscopic**

- These tumors can show a variety of growth patterns including insular, trabecular, and solid. Some authors refer to tumors showing an insular or trabecular growth pattern as “insular carcinomas.” Tumors may also show a characteristic “peritheliomatous” pattern of growth with extensive necrosis with preservation of viable cells around vessels. The tumor cells may show nesting or sheet-like growth with necrosis and vascular invasion frequently identified. The tumor cells are small and uniform with vesicular or hyperchromatic nuclei, small nucleoli, and prominent mitotic activity. Areas resembling papillary or follicular carcinomas are identified in some tumors, raising the possibility that these tumors may have dedifferentiated

**Immunohistochemical**

- These tumors are positive for thyroglobulin, low molecular weight kininogen, and TTF (see Table 11.1). If present TP53 nuclear staining is usually focal, and high Ki-67 index is common

**Molecular Genetics**

- Mutations of H-, K-, and N-RAS are identified in 50% of poorly differentiated carcinomas. Mutations of TP53 mutations are present in 20–30%, and p53 overexpression is present in 40–50%. A small percentage of tumors may show BRAF mutation, RET/PTC, or NTRK1 rearrangements

**Differential Diagnosis**

- Medullary thyroid carcinoma
  - Medullary thyroid carcinomas show neuroendocrine differentiation with stippled chromatin and are positive for chromogranin, synaptophysin, and calcitonin
- Follicular carcinoma
  - Follicular carcinomas lack the nuclear atypia, prominent mitotic figures, and necrosis seen in poorly differentiated thyroid carcinoma
- Solid variant of PTC
  - Poorly differentiated carcinomas often show prominent mitotic activity and areas of necrosis and lack the cytologic features classic of PTC
- Metastatic carcinomas to the thyroid
Poorly differentiated thyroid carcinomas are positive for TTF-1, a marker helpful in differentiating primary thyroid carcinomas from metastases, except those from the lung which also show positivity for TTF-1

Anaplastic Thyroid Carcinoma

Clinical
- Anaplastic (undifferentiated) thyroid carcinoma is a highly malignant tumor composed in part or entirely of undifferentiated cells with immunohistochemical and ultrastructural features supporting epithelial differentiation
- These tumors usually present as a rapidly expanding mass with symptoms of regional invasion (dysphagia, dyspnea, or dysphonia) in elderly patients. Females are affected more commonly than males (1.5:1)
- At surgery, invasion of adjacent structures including the neck muscles, trachea, esophagus, laryngeal nerve, and larynx are common. Almost half of all patients have distant metastases at diagnosis. The most common metastatic sites include lung, bone, and brain. These are highly aggressive tumors with a mortality rate of greater than 90% and a mean survival of 6 months

Macroscopic (Fig. 20.30)
- The tumors are grossly invasive, replace the thyroid, and extensively involve regional neck structures. The tumors have a white to tan cut surface and are firm to hard. Hemorrhage and necrosis are common

Microscopic (Fig. 20.31)
- The tumors can be composed of different cell types, sometimes in combination, including spindle cells, pleomorphic multinucleated and epithelioid cells. Mitotic activity, necrosis, and angiolymphatic invasion are often prominent.

Immunohistochemistry
- Anaplastic thyroid carcinomas show positivity for keratin, often low molecular weight keratin, although the staining is usually not strong and diffuse. These tumors are positive for vimentin and TP53. TTF-1 immunopositivity is focally seen. Strong diffuse staining for TTF-1 would favor a pulmonary metastasis over an anaplastic thyroid carcinoma

Molecular Genetics
- Anaplastic thyroid carcinomas may show overexpression of cyclin D1, inactivation of PTEN and p16, decreased expression of p27, TP53 mutation, β-catenin gene (CTNNB1) mutation, and chromosomal alterations

Differential Diagnosis
- Sarcoma
  - Anaplastic thyroid carcinomas can show prominent spindling and can be mistaken for sarcomas. Cytokeratin and focal TTF-1 immunostaining are helpful in confirming a diagnosis of anaplastic thyroid carcinoma
- B-cell lymphoma
  - Lymphomas can present as a rapidly growing thyroid mass. Primary thyroid lymphomas are often B-cell lymphomas and frequently arise in the setting of Hashimoto thyroiditis. Immunohistochemical studies can be useful in these cases
- Metastatic carcinomas to the thyroid
  - Metastases to the thyroid can be differentiated from anaplastic thyroid carcinoma with immunohistochemical studies. One caveat is that TTF-1 positivity in anaplastic thyroid carcinomas is usually quite focal, thus the
presence of strong diffuse TTF-1 positivity would favor a pulmonary metastases to the thyroid over a primary anaplastic thyroid carcinoma

C-Cell Hyperplasia

Clinical

Hyperplasia of C-cells is seen in association with (and thought to be precursor of) medullary thyroid carcinoma, although this may be seen in association with other tumors and conditions and as physiologic C-cell hyperplasia with over-stimulation by TSH. C-cell hyperplasia is commonly associated with multiple endocrine neoplasia (MEN) types 2A and 2B and familial medullary thyroid carcinoma. Patients with neoplastic C-cell hyperplasia usually undergo total thyroidectomy as it may progress to medullary thyroid carcinoma if untreated

Macroscopic

C-cell hyperplasia may not be evident grossly, although a few small 1- to 2-mm foci in the middle to upper portions of the thyroid lobes may be identified in familial disease. When a thyroidectomy has been performed in the setting of MEN2A, MEN2B, or familial medullary thyroid carcinoma, the gland should be serially sectioned with particular attention to the junction of the upper and middle one-third of the lobes as this is the area of highest concentration of C-cells and immunoperoxidase studies performed with chromogranin, synaptophysin, and calcitonin

Microscopic (Figs. 20.32 and 20.33)

C-cell hyperplasia is defined by an increase in the total mass of C-cells in the thyroid gland. C-cells can be increased in a diffuse or a nodular form. Nodular C-cell hyperplasia is described as clusters of more than 6 cells in several foci from both lobes. Diffuse C-cell hyperplasia describes an increase in C-cells measured as greater than 50 C-cells per low power field in both lobes

Immunohistochemistry

C-cells are positive for calcitonin, low molecular weight keratin (CAM 5.2), synaptophysin, chromogranin, and CEA. Hyperplastic C-cells tend to show greater CEA immunoreactivity than normal C-cells

Differential Diagnosis

Reactive and physiologic C-cell hyperplasia

- Reactive C-cell hyperplasia can be seen in lymphocytic thyroiditis, hyperparathyroidism, and adjacent to thyroid neoplasms. The significance of C-cell hyperplasia in patients without a family history of MEN or medullary thyroid carcinoma is unknown

Medullary thyroid microcarcinoma

- If C-cells are tumifactive, infiltrative, or there is a desmoplastic response, then they are best classified as a medullary thyroid carcinoma

Differential Diagnosis

Medullary Thyroid Carcinoma

Clinical

Medullary thyroid carcinoma (MTC) is a neuroendocrine carcinoma composed of C-cells. MTC accounts for 5–10% of thyroid malignancies

Patients usually present with a thyroid nodule, while some may present with metastatic disease. Approximately 50% of patients have metastases while diagnosis. Serum calcitonin levels are elevated and these tumors may be associated with ectopic hormone secretion (adrenocorticotropic hormone, histamine, insulin, serotonin, etc.)

Although the majority of MTC occur sporadically, approximately 25% are familial and associated with MEN2A, MEN2B, or familial MTC (FMTC). Patients with sporadic tumors present at an average age of 50 years, while those with familial tumors can present much earlier. Familial tumors are more often bilateral and multicentric. RET mutational analysis is recommended in patients diagnosed with MTC. If a patient has a RET mutation, then genetic testing is offered to the patient’s relatives.
Syndrome-associated MTC generally presents at an earlier age than sporadic cases. Patients with MEN 2A often present with MTC in early adulthood, while with patients with MEN 2B are often diagnosed as infants or children. FMTC usually presents at an older age than the other syndrome-associated MTC patients.

Patients with MTC are treated with total thyroidectomy and lymph node dissection for metastatic disease. These tumors are radioresistant and chemotherapy resistant and they do not take up reactive iodine. Five- and 10-year survival rates are 83.2% and 73.7%, respectively. Patients with familial tumors diagnosed by biochemical or molecular methods have a better prognosis than patients who are not screened. Poor prognostic factors include older age, male sex, clinical presentation (versus biochemical or molecular), metastatic disease, and high TNM stage. Widespread metastases may be associated with diarrhea, bone pain or flushing, and the five-year survival of about 10%.

**Macroscopic (Fig. 20.34)**

- MTC are usually nonencapsulated, firm, gray-white tumors that are gritty on cut section. Sporadic tumors are usually single and unilateral, while familial tumors are often multicentric and bilateral.

**Microscopic (Figs. 20.35–20.38)**

- Medullary thyroid carcinomas usually show infiltrative growth but may appear circumscribed. They are composed of round cells with granular amphophilic cytoplasm and round regular nuclei with coarse chromatin, growing in nests separated by vascular septa and hyalinized collagen.
- The tumor cells can be quite variable and show spindling, giant cells, mucin production, cytologic clearing, pigmentation, plasmacytoid cytomorphology, oncocytic features or can appear almost squamoid. These tumors may show a variety of growth patterns (trabecular, glandular, pseudopapillary).
- Amyloid (amorphous eosinophilic hyaline material) is classically seen in stroma, although some tumors do not have any visible amyloid. Calcification, sometimes coarsely laminated, may be present.
- The surrounding thyroid parenchyma may show C-cell hyperplasia.

![Fig. 20.34. Medullary carcinoma: Poorly demarcated tumor located at the upper pole of lateral lobe of thyroid.](image1)

![Fig. 20.35. Medullary carcinoma: Much solid, structureless eosinophilic material (amyloid) in a background of tumor cells without pattern.](image2)

![Fig. 20.36. Medullary carcinoma: Large aggregates of tumor cells create a carcinoid-like picture.](image3)
Immunohistochemistry

♦ The tumor cells are positive for calcitonin, chromogranin, synaptophysin, calcitonin gene-related peptides, keratin (cytokeratin 7, CAM 5.2), and TTF-1 and are negative for thyroglobulin. Other neuroendocrine peptides such as somatostatin, bombesin, and pro-opiomelanocortin may also be expressed. The immunostains may also highlight areas of C-cell hyperplasia in the surrounding thyroid parenchyma.

♦ Amyloid stains appropriately with various reagents (cresyl violet, sulfated alcian blue) demonstrate typical apple green birefringence with congo red under polarized light.

Molecular Genetics

♦ The heritable forms of medullary thyroid carcinoma, MEN 2A, MEN 2B, and FMTC, are autosomal dominant diseases caused by germline mutations in RET protooncogene. Thus, RET mutation testing is recommended for patients diagnosed with MTC. If the patient is found to be positive then their relatives are also offered testing. The vast majority of cases of MEN 2B are associated with germline mutation in RET protooncogene at codon 918 (>95%) or 883 (2–3%). MEN 2A and FMTC are associated with RET mutations involving codons 609, 611, 618, 620, and 634. FMTC can also be associated with mutations of 768, 790, 791, 804, 844, and 891, which are associated with later onset and less aggressive disease.

Variants

♦ Medullary thyroid microcarcinoma
  - Medullary thyroid microcarcinomas are defined as tumors less than 1 cm in diameter. They may be associated with elevated serum calcitonin, but are often discovered as incidental findings during surgery for thyroid nodules. Microcarcinomas have a much better prognosis than larger MTC, and lymph node metastases are rarely present at the time of surgery in patients with medullary microcarcinomas.

♦ Oncocytic/oxyphilic variant of MTC
  - MTC may show prominent Hürthle/oxyphilic cytologic changes, but the nuclear changes are of a neuroendocrine tumor. The finding of amyloid is also a helpful clue to the diagnosis of MTC.

Differential Diagnosis

♦ Papillary thyroid carcinoma
  - MTC may show papillary architectural features, but lack the classic cytologic features of PTC. Immunoperoxidase studies can be helpful as both are positive for TTF-1, but MTC are negative for thyroglobulin and are positive for chromogranin, synaptophysin, and calcitonin.

♦ Hürthle cell carcinoma
  - The oxyphilic/oncocytic variant of MTC can be confused with Hürthle cell neoplasms. Immunoperoxidase studies can be helpful as both are positive for TTF-1, but MTC are negative for thyroglobulin and are positive for chromogranin, synaptophysin, and calcitonin.

♦ Atypical laryngeal carcinoid
  - Both atypical laryngeal carcinoid and MTC are neuroendocrine tumors and both show positivity for chromogranin, synaptophysin, and calcitonin; thus TTF-1 is essential to differentiate these entities as atypical laryngeal carcinoid is negative and MTC is positive for TTF-1.

♦ Neuroendocrine lung tumors
  - Both MTC and neuroendocrine lung tumors are positive for TTF-1, cytokeratin 7, CAM 5.2, chromogranin, and synaptophysin, but neuroendocrine lung tumors are generally negative for calcitonin, a marker positive in MTC.
Introduction

Parathyroid glands produce parathyroid hormone (PTH), which is encoded by the PTH gene on 11p15. PTH promotes calcium entry into blood from bone, kidney, and gastrointestinal tract. PTH stimulates renal calcitrol synthesis, which promotes calcium and phosphorus absorption in the GI tract and stimulates osteoclasts to mobilize calcium from bone. PTH stimulates reabsorption of calcium in the kidney and phosphate clearance. Elevated calcium inhibits conversion of pre-pro-PTH to PTH. Low serum calcium is sensed by a calcium-sensing receptor (CASR) on the surface of parathyroid cells and results in PTH secretion, and high serum calcium inhibits PTH secretion.

The parathyroid glands are derived from the 3rd (inferior parathyroid glands and thymus) and 4th (superior parathyroid glands) branchial pouches. Most people have 4 parathyroid glands, but around 10% of people have >4 parathyroid glands, and a few have <3 parathyroid glands. Parathyroid glands can be identified ectopically in the thyroid, mediastinum, thymus, soft tissue behind esophagus and pharynx. Normal parathyroid glands are 4–6 mm in length and weigh 20–40 mg each. A parathyroid gland greater than 50–60 mg is considered abnormal. There is significant variation in cellularity even among glands in a single individual. Generally, parathyroid glands contain about 10–30% stromal fat. Stromal fat and connective tissue increase with age and vary with constitutional factors. Within a parathyroid gland, the polar regions have more stromal fat than the central aspect of the gland.

Parathyroid parenchymal cells include chief cells, oncocytic/oxyphilic cells, transitional cell, and clear cells. Chief cells are 10 μm, polyhedral, round central nuclei, eosinophilic to amphophilic cytoplasm, fat droplets (adults), and have well-defined cytoplasmic membranes. Oncocytic/oxyphilic cells are 10–20 μm, abundant eosinophilic cytoplasmic granules (mitochondria). Oncocytic cells appear at puberty, increase with age, and may form nodules. Clear cells are variably seen in normal and diseased parathyroid tissues.

Intraoperative PTH monitoring is a useful adjunct in confirming the removal of the diseased parathyroid gland or glands and decrease the risk of missing multiglandular disease. Intraoperative pathology assessment of parathyroid biopsies is done to confirm the specimen is parathyroid parenchyma (versus thyroid). Parathyroid cells are smaller and more vacuolated than thyroid and have round nuclei with dense chromatin and cytoplasmic lipid/fat droplets and well-defined cytoplasmic membranes.

Parathyroid Cyst

Clinical

Parathyroid cysts are relatively uncommon, may be nonfunctioning, and can present as a palpable nodule if large or local tenderness. Small microcysts are not uncommon incidental findings at autopsy. Functioning parathyroid cysts can be associated with hyperparathyroidism and may represent cystic degeneration of a parathyroid adenoma. Although parathyroid cysts are usually benign, parathyroid carcinoma has been reported in association with a parathyroid cyst.

Macroscopic (Fig. 20.39)

Parathyroid cyst is a solitary, thin walled, fluid-filled cyst, 1–6 cm in diameter, usually identified in the inferior glands, but may occur in the thyroid or mediastinum.

Microscopic (Fig. 20.40)

Parathyroid cysts have a thin wall lined by cuboidal epithelium with clear cytoplasm. The cyst wall often is associated with stromal fat.
with adjacent normal parathyroid tissue, but can contain lymphoid, muscular, thymic, adipose, and mesenchymal tissues

**Differential Diagnosis**

- Parathyroid adenoma
  - Large parathyroid adenomas can undergo cystic degeneration. Parathyroid adenomas are usually associated with laboratory evidence of hyperparathyroidism. Cystic parathyroid adenomas usually show residual adenoma in the tissue surrounding the cyst

- Thyroglossal duct cyst
  - Thyroglossal duct cysts are midline, at or above level of the thyroid, with thyroid tissue identifiable in the wall

- Branchial cleft cyst
  - Branchial cleft cysts are in the anterolateral neck. These cysts are lined by mixed squamous and respiratory epithelium and lack thyroid or parathyroid tissue

**Amyloid**

- Amyloid can be identified in parathyroids in patients with and without systemic amyloidosis. Amyloid can involve normal and diseased parathyroid glands. Amyloid is often intrafollicular and shows apple-green birefringence with Congo red stain

**Parathyroiditis**

- Parathyroiditis can be autoimmune associated and may result in hypoparathyroidism or hyperparathyroidism

**Glycogen Storage Diseases**

- Generalized glycogen storage diseases, such as Pompe disease (type II glycogenosis), affect many organ systems and can affect the parathyroid glands

**Parathyroid Hyperplasia**

**Clinical**

- Hyperparathyroidism is an increase in PTH, which results in increased serum calcium levels. Hyperparathyroidism is caused by parathyroid hyperplasia, parathyroid adenoma, and parathyroid carcinoma. Parathyroid hyperplasia is an enlargement of multiple parathyroid glands due to autonomous hyperplasia (primary chief cell hyperplasia) or in response to chronically low serum calcium (secondary chief cell hyperplasia). Hyperplasia accounts for 15% of primary hyperparathyroidism, is twice as common in women as it is in men, and is most common in the fifth decade. The incidence of parathyroid hyperplasia has increased with the utilization of screening calcium levels in asymptomatic patients. Historically, patients presented with clinical signs and symptoms such as osteopenia and nephrocalcinosis

- Parathyroid hyperplasia can be hereditary in multiple endocrine neoplasia (MEN) type 1, MEN2A, familial hypocalciuric hypercalcaemia, neonatal severe primary hyperparathyroidism, hyperparathyroidism-jaw tumor syndrome, and familial isolated hyperparathyroidism

- Parathyroid hyperplasia is the most common manifestation of MEN1. Parathyroid hyperplasia associated with MEN1 occurs around 20 years of age, which is much earlier than sporadic hyperplasia. In addition to parathyroid hyperplasia, MEN1 is also associated with pituitary adenomas, neuroendocrine tumors of the pancreas, duodenum, thymus and lung, gastrinomas, adrenal cortical adenomas and hyperplasia, cutaneous angiofibromas, collagenomas, and café au lait macules, lipomas, gingival papules, meningiomas, ependymomas, and leiomyomas

- Approximately 20–30% of cases of MEN2A are associated with parathyroid hyperplasia and or adenomas. Other features of MEN2A include medullary thyroid carcinoma and pheochromocytoma

- Other causes of familial hyperparathyroidism are familial hypocalciuric hypercalcaemia and neonatal primary hyperparathyroidism, which are caused by a mutation in the CASR gene. Hyperparathyroidism jaw tumor syndrome is an autosomal dominant disorder associated with parathyroid hyperplasia or adenoma, fibroosseus jaw tumors, renal cysts, hamartomas, Wilms tumors, and an increased incidence of parathyroid carcinoma. Familial isolated hyperparathyroidism accounts for 1% of primary hyperparathyroidism and has an increased risk of parathyroid carcinoma

- Secondary parathyroid hyperplasia has increased PTH due to low serum calcium caused by disorders of phosphate metabolism, vitamin D deficiency, tissue resistance to vitamin D, and malabsorption. The most common cause of secondary hyperparathyroidism is chronic renal failure. Patients with secondary hyperparathyroidism can develop an autonomously functioning parathyroid gland (tertiary hyperparathyroidism)

**Macroscopic (Fig. 20.41)**

- Parathyroid hyperplasia shows enlargement of multiple parathyroid glands (up to 10g each). Sporadic and hereditary forms of primary parathyroid hyperplasia are histologically indistinguishable, but primary hyperplasia may show more nodular enlargement of parathyroid glands, while secondary hyperplasia may show a more diffuse pattern of enlargement. Depending on degree of hypocalcemia, secondary chief cell hyperplasia is more variable in appearance, with glands ranging from normal size to moderately enlarged size (up to 6 g each)

- One must be cautious in evaluating parathyroid glands in relation to size and cellularity as these parameters can vary greatly even within a single patient. An asymmetrically enlarged gland can be misinterpreted as a parathyroid adenoma. Communication between the pathologist and surgeon is critical for the appropriate interpretation

**Microscopic (Fig. 20.42)**

- Parathyroid hyperplasia principally involves chief cells, although other cells types (oxyphil, water-clear, and transitional) may be involved. Cells grow in large hyperplastic nodules scattered throughout gland (nodular hyperplasia),
giving it an irregular, asymmetrical appearance. Diffuse
growth may also be seen, especially in young patients. The
cells can show sheet-like growth, palisading, glandular for-
mations, cribriform growth, papillary areas, fibrosis, and
cystic change

**Immunohistochemistry**

- Hyperplastic parathyroid tissues are positive for the same
  immunohistochemical markers as normal parathyroid
tissue: chromogranin A, synaptophysin, low molecular
weight keratins, and PTH. Parathyroid tissue is negative
for TTF-1, which is helpful in separating it from thyroid
tissue

**Molecular Genetics**

- Parathyroid hyperplasia is usually polyclonal, although areas
  of monoclonality can be identified in nodular areas. Genetic
  abnormalities have not been well-defined in sporadic hyper-
parathyroidism, although more is known about the genes
associated with in hereditary hyperparathyroidism such as
MEN1, RET, CASR, among others

- Germline MEN1 mutations are identified in 80–94% of
  patients with familial MEN1 and 65–88% with sporadic
MEN1. MEN1 is a tumor suppressor gene on chromosome
11q13 that encodes menin, a protein that is truncated or
absent when MEN1 is mutated. MEN1 is an autosomal
dominant disorder with high penetrance, but it can occur
sporadically from new mutations. Over 1,000 different
MEN1 mutations have been identified. The detection rate of
MEN1 mutation increases with the number of MEN1 related
tumors and family history of MEN1, as sporadic cases can
be due to somatic mosaicism

- Approximately 95% of MEN2A families have a RET muta-
tion in exon 10 or 11. RET protooncogene (10q21) encodes
a plasma membrane tyrosine kinase involved in cell growth
and differentiation. The majority of mutations involve codon
634, which is associated with high penetrance

- The CASR is present in parathyroid, kidney, thyroid C-cells,
  intestine, and bone. Calcium sensing receptors sense extra-
cellular calcium levels, which inversely regulates the release
of PTH. An inactivating mutation in the CASR gene (3q13.3-
21) results in decreased calcium sensitivity and excess PTH
secretion. Heterozygous inactivating CASR mutations occur
in familial hypocalciuric hypercalcemia, and homozygous
inactivating mutations occur in neonatal severe hyperpara-
thyroidism. Hypocalciuric hypercalcemia is due autoanti-
bodies against CASR and can simulate familial hypocalciuric
hypercalcemia

- The HRPT2 gene mapped to 1q25-q32 encodes parafibro-
min. HRPT2 is a putative tumor-suppressor gene, the inacti-
vation of which is involved in HPT-JT syndrome and some
sporadic parathyroid tumors

**Variants**

- Clear cell hyperplasia (Figs. 20.43 and 20.44)
  - Clear cell hyperplasia is a rare sporadic variant of para-
thyroid hyperplasia with marked parathyroid enlarge-
cement (combined weights may be >100 g) and associated
primary hyperparathyroidism. The enlargement is usually
asymmetric, with upper glands larger than lower glands.
The cells have a diffuse or alveolar growth pattern. The
cells are large and ballooned, with finely vacuolated
water-clear showing marked size variation

- Lipohyperplasia
  - Lipohyperplasia is another rare variant of parathyroid
hyperplasia that can occur sporadically or with familial
benign hypocalciuric hypercalcemia
Endocrine Pathology

Fig. 20.44. Wasserhelle hyperplasia: Very large parathyroid cells with clear cytoplasm are sharply outlined and have generally central nuclei.

Fig. 20.43. Wasserhelle hyperplasia: Three glands are enlarged (the right superior and right inferior glands were fused). The cut surfaces are brown. Total parathyroid weight = 2.5 g.

Differential Diagnosis

♦ Parathyroid adenoma
  - Parathyroid adenoma generally involves only a single gland, with other glands usually appearing atrophic.

Parathyroid adenoma is an encapsulated cellular nodule compressing normal, sometimes atrophic, rim of parathyroid tissue

Parathyroid Adenoma

Clinical

♦ Parathyroid adenoma is a benign parathyroid neoplasm, affecting a single gland, composed of chief, oncocytic, transitional, water clear, or mixtures of cells

♦ Parathyroid adenoma is the most common cause of hyperparathyroidism (80% of cases)

♦ Parathyroid adenomas are more common in women (3:1) than in men and are usually too small and soft to be identified on physical examination. Parathyroid adenomas can be seen at any age, but are commonly identified in the 4th decade

♦ Parathyroid adenomas occur in ectopic locations 10% of the time

♦ The majority of parathyroid adenomas are hormonally active. Most cases are identified by elevated serum calcium levels. Historically patients were identified because of clinical symptoms. Serum calcium levels are elevated in parathyroid adenoma, but not as markedly elevated as is seen in parathyroid carcinoma

Macroscopic (Fig. 20.45)

♦ Grossly, parathyroid adenoma is a small, slightly lobulated nodule, weighing 0.5–5 g, with a delicate capsule. Parathyroid adenomas have a smooth, shining exterior, without adjacent tissues attached. They are gray-brown in color, with soft consistency. Other parathyroid glands should appear normal or atrophic

Fig. 20.45. Parathyroid adenoma: Cut surface of oval enlarged parathyroid gland is tan. Weight = 2.07 g.
Microscopic (Figs. 20.46–20.50)

- Microscopically, parathyroid adenoma is an encapsulated nodule of highly cellular parathyroid tissue. The growth pattern is usually solid, but follicles or papillary structures can be seen. Parathyroid adenomas are composed predominantly of chief cells, but other cell types can be seen.
- A rim of compressed normal tissue is identified in 50–60% of parathyroid adenomas, but the chance of identifying a rim of normal decreases as the size of the tumor increases.
- Areas of nuclear pleomorphism (endocrine atypia) may be noted as well as rare mitotic figures. Prominent mitotic activity would be worrisome for parathyroid carcinoma (Table 20.2).

Immunohistochemistry

- Parathyroid adenomas have an identical immunohistochemical staining pattern to that of normal parathyroid chief cells with positivity for chromogranin, synaptophysin, and parathyroid hormone, and negative for TTF-1.

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Fig. 20.46. Parathyroid adenoma: A mantle of normal parathyroid surrounds a sheet of adenoma cells.

Fig. 20.47. Parathyroid adenoma: Tumor composed of chief cells features oxyphil cell nodules with eosinophilic cytoplasm.

Fig. 20.48. Parathyroid adenoma: Adenoma features trabeculae of cells with clear cytoplasm and basal nuclei, supported by a delicate capillary network.

Fig. 20.49. Parathyroid adenoma: The adenoma features scattered multinucleated cells set in a background of cells with oxyphilic cytoplasm.

Fig. 20.50. Parathyroid adenoma: Oxyphil tumor with sharply outlined cells and clear granular eosinophilic cytoplasm.
Table 20.2. Parathyroid Carcinoma vs. Adenoma

<table>
<thead>
<tr>
<th></th>
<th>Parathyroid adenoma</th>
<th>Parathyroid carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>Unusual</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>Elevated</td>
<td>Markedly elevated (&gt;13 mg/dL)</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Can overlap in size</td>
<td>Larger</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Invasion into adjacent structures</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Metastases</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Growth pattern</td>
<td>Patterns (acinar, follicular)</td>
<td>Monotonous</td>
</tr>
<tr>
<td>Cellular features</td>
<td>Often mixed cell types, “endocrine atypia”</td>
<td>Often monotonous, prominent nucleoli</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Can have mitoses, but infrequent</td>
<td>Yes (higher mitotic rate than adenomas)</td>
</tr>
<tr>
<td>Fibrous bands</td>
<td>Can be seen due to degenerative changes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Molecular Genetics

- A number of genes thought to be important in parathyroid tumorigenesis are located on chromosome 11. Cyclin D1 is a regulator of cell cycle progression from G1 to S phase. Encoded by the cyclin D1/PRAD1 (parathyroid adenoma) gene on chromosome 11q13, cyclin D1 overexpression has been observed in neoplastic parathyroid glands. Genetic alterations in cyclin D1/PRAD1 gene have been found in approximately 5% of parathyroid adenomas.

- The MEN1 tumor suppressor gene is located in the region of 11q13. Loss of heterozygosity (allelic losses) in this region is known to be frequent in parathyroid adenomas, but not carcinomas. Also, patients with MEN1 associated familial parathyroid disease rarely develop parathyroid carcinoma. Deletion of 11q23 has also been reported to be frequently lost in parathyroid adenomas and occasionally in parathyroid hyperplasias suggesting the possibility of a tumor suppressor gene at this site.

Variants

- Ectopic parathyroid adenoma
  - Parathyroid adenomas are located in ectopic locations in approximately 10% of cases. Locations include intrathyroidal, mediastinum, thymus, and soft tissue behind esophagus and pharynx. Intrathyroidal parathyroid adenomas are usually derived from the superior parathyroid glands. Intrathyroidal adenomas are often partly in the thyroid capsule or in a cleft in the thyroid surface rather than being truly intrathyroidal. Thymus or mediastinal parathyroid adenomas usually derive from the inferior parathyroid glands.

- “Double” parathyroid adenomas
  - Double parathyroid adenomas are exceptionally rare. Most cases are later found to be asymmetric parathyroid hyperplasia. Occasionally, glands involved by parathyroid hyperplasia may show rims of normal parathyroid tissue. A diagnosis of “double” or “triple” parathyroid adenomas would require resolution of hypercalcemia and hyperparathyroidism and long-term followup to be certain that no other glands involved.

Oxyphil adenoma

- Oxyphil adenoma is a benign encapsulated neoplasm composed exclusively or predominantly (more than 90%) of mitochondrion-rich oncocyes (Fig. 20.50). Oxyphil adenomas comprise 3–6% of parathyroid adenomas, and are usually functional.

- Oxyphilic parathyroid adenomas and carcinomas must be distinguished from Hürthle cell thyroid neoplasms. Parathyroid tissues have very well-defined cytoplasmic membranes, lack colloid, and are positive for PTH, chromogranin, and synaptophysin and negative for TTF-1 and thyroglobulin.

Clear cell adenoma

- Clear cell adenoma is a benign encapsulated neoplasm composed exclusively or predominantly of large polyhedral cells with distinct plasma membranes and extensively vacuolated (water-clear) cytoplasm. Clear cell parathyroid adenomas are an exceeding rare cause hyperparathyroidism.

- Clear cell adenoma must be differentiated from hyperplasia with clear cell change, which is more common than clear cell adenomas. Multiple glands are involved in hyperplasia with clear cell change. The absence of normalization of PTH suggests that a putative clear cell parathyroid adenoma may be a normal parathyroid or hyperplasia with clear cell change.

Lipoadenoma (Figs. 20.51 and 20.52)

- Lipoadenoma is an encapsulated nodular growth composed of islands or cords of chief cells separated by abundant adipose tissue. Parachymal chief or oxyphil cells are arranged in anastomosing trabeculae or acinar formations.

Differential Diagnosis

- Parathyroid hyperplasia
  - Parathyroid hyperplasia involves multiple parathyroid glands. Distinguishing parathyroid adenoma from...
hyperplasia usually necessitates examination of at least one additional gland, which should be normal in cases of parathyroid adenoma. Microscopically, the parathyroids in hyperplasia appear diffusely enlarged, with an even distribution of cellularity and adipose tissue

♦ Atypical parathyroid adenoma
  - Atypical parathyroid adenomas show some worrisome features including mitotic activity and fibrous bands, but lack unequivocal invasion. Atypical parathyroid adenomas usually behave in an indolent manner

♦ Parathyroid carcinoma
  - Parathyroid carcinomas may be palpable, are often symptomatic, large, and are associated with higher serum calcium (13–15.5 mg/dL) than parathyroid adenomas. Parathyroid adenomas, particularly atypical parathyroid adenomas, can be very difficult to distinguish from carcinomas. Parathyroid carcinomas usually show monotonous growth rather than acinar and follicular growth patterns of adenomas. Mitotic figures can be seen in both, but are more numerous in carcinomas. Fibrous bands are concerning, but can be seen in both adenomas and carcinomas (Table 20.2)
  - The diagnosis of parathyroid carcinoma requires invasive growth or metastases, features not seen in parathyroid adenoma or atypical parathyroid adenoma

Parathyroid Carcinoma

Clinical

♦ Parathyroid carcinoma is a malignant epithelial tumor composed of parathyroid cells. Parathyroid carcinoma accounts for less than 1% of cases of hyperparathyroidism. These tumors usually occur in middle aged and older adults, but can occur over a wide age range. Females and males are equally affected. The majority of parathyroid carcinomas are sporadic, but there is an increased incidence of parathyroid carcinoma in patients with hyperparathyroidism jaw tumor syndrome

♦ Patients with parathyroid carcinoma are usually symptomatic with fatigue, weakness, weight loss, nausea, polyuria, or polydypsia and may have a palpable mass

♦ Most parathyroid carcinomas are functional, and patients have a markedly elevated serum calcium (13–15.5 mg/dL), PTH, and alkaline phosphatase. Because of the markedly elevated serum calcium, patients can present with nephrolithiasis, nephrocalcinosis, renal insufficiency, and may have bone disease

♦ Parathyroid carcinoma is treated by en bloc resection of the parathyroid tumor and the surrounding structures, including the ipsilateral thyroid lobe. Tumors often recur before they metastasize to the cervical and mediastinal lymph nodes, lungs, bone, and liver. Death is usually due to uncontrollable hypercalcemia. Survival at 5 years and 10 years is 85% and 49%, respectively

♦ Patients treated with surgery and postoperative radiation have decreased risk of locoregional disease progression and improved cause-specific survival

Macroscopic (Fig. 20.53)

♦ Parathyroid carcinoma is usually a firm mass adherent to regional structures. The tumor ranges from 1 to 6 cm (mean 3 cm) in size and weighs 1.5–30 g (mean 6.7 g). Parathyroid carcinomas are larger than parathyroid adenomas, but the tumors can overlap in size

Microscopic (Figs. 20.54–20.56 and Table 20.2)

♦ The histologic diagnosis of parathyroid carcinoma can be difficult. Parathyroid carcinomas usually have a monotonous, solid growth with sheets of cells. Prominent patterns, follicular and acinar, are not often seen. The cellular constituency is usually chief cells, but tumor can be composed
Fig. 20.53. Parathyroid carcinoma: Very ragged coarsely lobulated tumor.

Fig. 20.54. Parathyroid carcinoma: Tumor composed of variable-sized masses of subtly invasive parathyroid cells.

Fig. 20.55. Parathyroid carcinoma: Nodules of invasive tumor are present in the cervical fat.

Fig. 20.56. Parathyroid carcinoma: Well-differentiated tumor with sharply outlined regular cells. Mitosis is present.

Prominent nucleoli are often seen in parathyroid carcinoma, but cellular and nuclear pleomorphism is not diagnostic of parathyroid carcinoma. Parathyroid carcinomas show prominent mitotic activity, thick fibrous bands, and may show necrosis. Mitotic activity can be seen in parathyroid adenomas, although carcinomas generally have higher mitotic rates than adenomas and higher proliferative indices (Ki-67). Parathyroid adenomas can show degenerative changes with cells trapped within the capsule and fibrous bands. Features diagnostic of malignancy include vascular invasion, perineural invasion, invasion into adjacent structures and metastases.

Local recurrence of a previously diagnosed “parathyroid adenoma” is also a worrisome feature, but other explanations must be taken into account including parathyromatosis.

**Immunohistochemistry**

- Parathyroid carcinomas are positive for chromogranin, synaptophysin, parathyroid hormone, and keratin (CAM 5.2) and are negative for TTF-1 and thyroglobulin (Table 20.3)
- The cyclin-dependent kinase inhibitor protein p27 shows decreased expression in parathyroid carcinomas compared with parathyroid adenomas. An immunophenotype of positive staining for p27, bcl-2, mdm2, and negative staining for Ki-67 is more common in typical and atypical adenomas than in parathyroid carcinomas. Parafibromin is discussed under molecular genetics.
Inactivating mutations of the tumor suppressor HRPT2 gene (1q21-q32), which is responsible for the HPT-JT syndrome, have been implicated in a high proportion of parathyroid carcinomas. Germline mutations of the HRPT2 gene can be seen in a subset of patients with mutation-positive carcinomas. The HRPT2 gene is involved in both the hyperparathyroidism-jaw tumor syndrome and a subset of cases of familial isolated hyperparathyroidism. Sporadic parathyroid carcinomas have been found to have acquired inactivation of HRPT2, a finding very uncommon in parathyroid adenomas. This finding suggests that some patients with apparent sporadic parathyroid carcinomas may have the HPT-JT syndrome or a variant of this syndrome.

The HRPT2 gene encodes parafibromin. Loss of nuclear parafibromin immunoreactivity has been identified in parathyroid carcinomas as well as adenomas associated with HRPT2 mutation. Several studies have examined whether loss of nuclear parafibromin expression can be helpful in the diagnosis of parathyroid carcinoma. This marker shows some promise; however, the reproducibility and variability in the interpretation of this immunostain needs to be confirmed. Additionally, distinguishing parathyroid adenoma from carcinoma is less problematic than distinguishing atypical parathyroid carcinomas from parathyroid adenomas, but this marker has not yet been evaluated in this situation.

Cyclin D1 is a regulator of cell cycle progression from G1 to S phase. Encoded by the cyclin D1/PRAD1 (parathyroid adenoma) gene on chromosome 11q13, cyclin D1 overexpression has been observed in neoplastic parathyroid glands. Genetic alterations in cyclin D1/PRAD1 gene have been found in approximately 5% of parathyroid adenomas.

*p53* gene on chromosome 17p13.1 is the most common genetic alteration in human cancers, but differentiated endocrine malignancies usually have a low frequency of *p53* mutation. Allelic loss of the *p53* gene has been noted parathyroid carcinomas, but without great frequency.

The MEN1 tumor suppressor gene is located in the region of 11q13. Loss of heterozygosity (allelic losses) in this region is known to be frequent in parathyroid adenomas, but not carcinomas. Also, patients with MEN1 associated familial parathyroid disease rarely develop parathyroid carcinoma. Deletion of 11q23 has also been reported to be frequently lost in parathyroid adenomas and occasionally in parathyroid hyperplasias suggesting the possibility of a tumor suppressor gene at this site.

### Differential Diagnosis

- **Parathyroid adenoma**
  - Parathyroid adenomas generally are asymptomatic, while parathyroid carcinomas are more often associated with clinical symptoms. Parathyroid carcinoma may be associated with a palpable mass, a feature highly unusual for a parathyroid adenoma. Serum calcium levels in parathyroid adenomas usually are not as markedly elevated as those in patients with parathyroid carcinomas, who may have serum calcium levels 13–15.5 mg/dL. Parathyroid adenomas are usually smaller than carcinomas, but there can be overlap in size. Parathyroid adenomas lack the invasive growth that is diagnostic of parathyroid carcinoma.

- **Atypical parathyroid adenoma**
  - Atypical parathyroid adenomas are noninvasive parathyroid neoplasms composed of chief cells with variable numbers of oncocyes and transitional oncocyes, with some of the features of parathyroid carcinoma but lacking unequivocal capsular, vascular, or perineural space invasion or metastases. These tumors may show adherence to adjacent structures, mitotic activity, fibrosis, trabecular growth pattern, and tumor cells within the capsule, but they lack invasive growth.

- **Parathyroid hyperplasia**
  - Parathyroid hyperplasia involves multiple glands. The glands in hyperplasia lack the infiltrative growth diagnostic of parathyroid carcinoma.

- **Parathyromatosis**
  - Parathyromatosis is generally not associated with a palpable neck mass or the degree of hypercalcemia seen in

### Table 20.3. Parathyroid Carcinoma Differential Diagnosis

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Chromogranin</th>
<th>Synaptophysin</th>
<th>Parathyroid hormone</th>
<th>Thyroglobulin</th>
<th>TTF</th>
<th>Calcitonin</th>
</tr>
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<tbody>
<tr>
<td>Parathyroid carcinoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Follicular, Hürthle, or papillary thyroid carcinoma</td>
<td>–</td>
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<tr>
<td>Medullary thyroid carcinoma</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>Metastatic carcinoma</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

*Metastatic carcinomas from particular sites, such as lung, can show positivity for thyroid transcription factor (TTF)
parathyroid carcinoma. Unlike parathyroid carcinoma, parathyromatosis lacks vascular invasion, infiltrative growth, and significant mitotic activity.

- Thyroid neoplasms
  - Parathyroid cells show well-defined cytoplasmic membranes and lack the colloid seen in thyroid tissues. In difficult cases, immunoperoxidase studies can be very helpful in separating these entities as parathyroid tissue is positive for synaptophysin, chromogranin, and PTH and negative for TTF-1 and thyroglobulin. Thyroid follicular tumors are positive for TTF-1 and thyroglobulin and negative for chromogranin, synaptophysin, and parathyroid hormone. Similar to parathyroid carcinoma, medullary thyroid carcinoma is positive for synaptophysin and chromogranin, but medullary thyroid carcinomas are also positive for TTF and calcitonin and negative for PTH.

**Parathyromatosis**

**Clinical**
- Parathyromatosis is a rare cause of hyperparathyroidism. It is caused by inadvertent autotransplantation of tissue from previous operations or hyperfunction of tissue left behind during organogenesis.

**Macrosopic**
- Nodules of parathyroid tissue are present in fibrofatty tissue

**Microscopic**
- Nodules of hyperfunctioning chief cells with well-defined cytoplasmic membranes and lacking prominent mitotic activity are identified in fibrous tissue or fibrofatty tissue. The nests of cells lack highly infiltrative growth pattern

**Immunophenotype**
- Parathyromatosis shows positivity for neuroendocrine markers chromogranin and synaptophysin and is positive for PTH and cytokeratin (CAM 5.2) and negative for TTF.

**Differential Diagnosis**
- Parathyroid carcinoma
  - Unlike parathyromatosis, parathyroid carcinoma may present as a palpable neck mass and significant hypercalceemia. Parathyromatosis lacks the vascular invasion, infiltrative growth, and mitotic activity seen in parathyroid carcinoma.

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**ADRENAL GLAND**

**Adrenal Heterotopia**

**Clinical**
- Adrenal heterotopia is a benign congenital anomaly with normal adrenal tissue appearing in abnormal locations. This condition is relatively common, as it has been seen in up to 30% of autopsies. The ectopic tissue is usually located in retroperitoneal space near the adrenals and kidneys, in the pelvis, or in the inguinal area. The ectopic tissue may undergo hyperplasia in response to increased ACTH levels and rarely may give rise to cortical neoplasms.

**Macroscopic**
- Grossly, adrenal heterotopias are small (<1 cm) nodules of yellow tissue resembling normal adrenal cortex.

**Microscopic**
- Most adrenal heterotopias consist of adrenal cortical tissue only, but some may also contain medulla.

**Immunohistochemistry**
- Adrenal heterotopias have identical staining pattern to normal adrenal tissues.

**Focal Adrenalitis**

**Clinical**
- Focal adrenalitis is identified in up to 50% of autopsy patients, and is particularly common in the elderly.

**Microscopic (Fig. 20.57)**
- Perivascular aggregates of lymphocytes and plasma cells are identified in the cortical and medullary tissue.

**Differential Diagnosis**
- Autoimmune adrenalitis
  - Inflammatory response is more diffuse in autoimmune adrenalitis than the foci of lymphocytes and plasma cells seen in focal adrenalitis. Autoimmune adrenalitis is asso-
associated with marked cortical atrophy, a feature not seen in focal adrenalitis

- Adrenal aplasia
  - Adrenal aplasia is unilateral or bilateral absence of adrenal gland, usually in setting of multiple congenital anomalies such as acardia, anencephaly, and renal agenesis

**Adrenal Cysts**

**Clinical**

- Adrenal cysts are uncommon, usually incidental findings on CT or MRI, but can be symptomatic. The majority of adrenal cysts are benign, but adrenal cysts can be identified with adrenal neoplasms, both benign and malignant. Adrenal cysts are generally seen in adults in the fourth to sixth decades

- In a recent study from Mayo Clinic, 41 macroscopically cystic lesions were identified over a 25-year period. Of these 41 cases, 32 were pseudocysts, 8 were endothelial cysts, and 1 was an epithelial cyst. Of the 32 pseudocysts, 6 were associated with adrenal neoplasms (2 adrenal cortical carcinomas, 2 adrenal cortical adenomas, and 2 pheochromocytomas). One pheochromocytoma case was identified with an endothelial cyst. Both patients with cystic adrenal cortical carcinomas died of disease

**Macroscopic**

- Fluid-filled cysts range in size from 2 to 10 cm. The cyst wall may be focally calcified. The wall should be extensively sampled to search for an associated adrenal neoplasm

**Microscopic (Figs. 20.58 and 20.59)**

- Adrenal cysts are classified as pseudocysts, endothelial cysts, epithelial cysts, and infectious cysts

- The cyst walls are composed of fibrous tissue or have a lining of endothelial or epithelial cells. The wall often contains hemosiderin and elastic tissue. The wall needs to be carefully evaluated to be certain that the cyst is not associated with an adrenal neoplasm

**Differential Diagnosis**

- Adrenal cortical neoplasm or pheochromocytoma with cystic degeneration
  - Adrenal adenoma, adrenal carcinoma, and pheochromocytoma may undergo cystic degenerative changes that grossly mimic an adrenal cyst

**Adrenal Cytomegaly**

**Clinical**

- Adrenal cytomegaly is an incidental histologic finding in up to 3% of newborns and in 6.5% of stillborn fetuses. Adrenal cytomegaly is particularly prominent in the adrenal glands infants with Beckwith–Wiedemann syndrome

**Microscopic (Fig. 20.60)**

- The adrenal cortical cells are markedly enlarged cells (up to 120 μm) with prominent nuclear enlargement, hyperchromasia, and pleomorphism. Nuclear cytoplasmic inclusions can be seen
Beckwith–Wiedemann Syndrome

Clinical

♦ Beckwith–Wiedemann syndrome is a congenital disorder, sometimes familial, manifested by craniofacial abnormalities, abdominal wall defects, gigantism, macroGLOSSIA, and adrenal hyperplasia. The estimated incidence is 1 in 13,000 births. About 7.5% of affected children develop a malignant neoplasm (nephroblastoma or adrenal cortical carcinoma).

Macroscopic

♦ The adrenal glands are enlarged (up to 16 g) and have a cerebriform appearance.

Microscopic

♦ Microscopically, the cells show marked cytomegaly affecting nearly all the cells of cortex. Cortical microcysts may be seen. The medullary tissue may be hyperplastic.

Adrenal Leukodystrophy

Clinical

♦ Adrenal leukodystrophy is an X-linked metabolic disorder characterized by spastic paraplegia and adrenal insufficiency culminating in Addison disease.

Macroscopic (Fig. 20.61)

♦ Grossly, the adrenal cortex is atrophic.

Microscopic (Fig. 20.62)

♦ The cortex is attenuated and consists of ballooned cells with abundant granular or hyaline eosinophilic cytoplasm. Cells may have clear cytoplasm with intracytoplasmic striations.

Congenital Adrenal Hyperplasia (Adrenogenital Syndrome)

Clinical

♦ Congenital adrenal hyperplasia is a pathologic manifestation of group of autosomal recessive disorders characterized by enzymatic defects in cortisol synthesis. Insufficient cortisol results in increased ACTH secretion and subsequent bilateral adrenal hyperplasia. Biosynthesis pathway blockages result in shunting of steroids into other pathways, usually those for sex steroids. This disorder usually presents in first few years of life with abnormal hormone levels (sexual development abnormalities, hypertension, adrenal insufficiency, sodium imbalances). The most common enzymatic defect is 21-hydroxylase deficiency (seen in >90% of cases). Patients affected with longstanding disease may develop steroid neoplasms (adrenal cortical and testicular) because of stimulatory effects of chronically increased adrenocorticotropic hormone (ACTH) levels.

Macroscopic

♦ The adrenal glands show marked diffuse enlargement, each weighing 10–15 g, with a cerebriform appearance and tan-brown color.

Microscopic (Fig. 20.63)

♦ The zona fasciculata shows marked hyperplasia. Compact cells with eosinophilic cytoplasm (lipid-depleted) replace normal vacuolated (lipid-laden) fasciculata cells.

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Fig. 20.61. Adrenal leukodystrophy: Slices of adrenal gland biopsy in adrenoleukodystrophy shows much replacement of the yellow cortex by black and brown nodules.

Fig. 20.62. Adrenal leukodystrophy: Ballooned cortical cells with somewhat clear cytoplasm and intracytoplasmic striations.

Fig. 20.63. Congenital adrenal hyperplasia: Normal cortex replaced by clear-cell nodules.
Differential Diagnosis
♦ Adrenal cortical hyperplasia
  – Usually older patients are affected by adrenal cortical hyperplasia
♦ Hormonal syndromes usually associated with glucocorticoid or mineralocorticoid excess, rather than sex steroid excess
  – Commonly, nodular or mixed diffuse and nodular hyperplasia are seen
♦ Beckwith–Wiedemann syndrome
  – Beckwith–Wiedemann syndrome is associated with multiple anatomic anomalies. The adrenal glands show marked cortical cytomegaly

Primary Adrenal Insufficiency (Idiopathic Addison Disease)
Clinical
♦ Primary adrenal insufficiency is an autoimmune disease where antibodies directed against adrenal antigens result in cortical cell destruction and subsequent adrenal insufficiency. Adults are usually affected. The disorder is more common in females (F:M = 2:1) than in males. Patients manifest signs and symptoms of deficiencies in glucocorticoids and mineralocorticoids, including fatigue, weight loss, hypotension, poor stress tolerance, and increased pigmentation (due to increased ACTH). Primary adrenal insufficiency can be associated with autoimmune disease of thyroid (Hashimoto thyroiditis resulting in hypothyroidism), stomach (chronic atrophic gastritis resulting in pernicious anemia), or pancreas (inflammation of islets causing diabetes mellitus)

Macroscopic (Fig. 20.64)
♦ Grossly the adrenal glands show marked cortical atrophy

Microscopic (Fig. 20.65)
♦ Microscopically, the cortex is atrophic and has a lymphocytic infiltrate, while the medulla is uninvolved. The residual cortical cells are hypertrophied and have compact eosinophilic cytoplasm and enlarged nuclei (ACTH stimulation effect)

Differential Diagnosis
♦ Other causes of adrenal cortical insufficiency
  – Infectious agents such as mycobacteria, fungi, or viruses
  – Amyloid deposition
  – Adrenal hemorrhage (Waterhouse–Friderichsen syndrome)
  – Metastatic tumor
  – Pituitary lesions (tumor, necrosis, hemorrhage)

Secondary Adrenal Insufficiency
Clinical
♦ Secondary adrenal insufficiency is usually due to pituitary disease such as pituitary neoplasm or post-partum necrosis (Sheehan syndrome), which results in adrenal cortical atrophy due to lack of ACTH stimulation

Differential Diagnosis
♦ Exogenous steroid administration

Adrenal Cortical Hyperplasia
Clinical
♦ Adrenal cortical hyperplasia is characterized by enlargement of adrenal cortex with increased serum cortisol, usually due to increased stimulation by ACTH, either from pituitary or ectopic
Endocrine Pathology

sources. Patients may present with extra-adrenal tumor (ectopic ACTH secretion) or with symptoms of hypercortisolism.

The most common sources of ACTH include pituitary adenoma (Cushing disease), small cell lung carcinoma, carcinoid tumor (lung, gastrointestinal tract, thymus, or pancreas), islet cell carcinoma, and medullary thyroid carcinoma.

Macroscopic (Fig. 20.66)

♦ The adrenal cortex is enlarged either diffusely or in a nodular pattern. Diffuse hyperplasia results in moderate enlargement (12–24 g each) with uniform widening of cortex, which appears tan-brown. Nodular hyperplasia shows nodules in the cortex, which measures up to 3 cm, and adrenals may weigh up to 50 g. Diffuse and nodular hyperplasia may coexist in the same patient.

Microscopic (Fig. 20.67)

♦ Diffuse hyperplasia microscopically is characterized by expanded zona fasciculata with compact, lipid-depleted cells, and the zona glomerulosa cells appear vacuolated.

♦ Nodular hyperplasia (Figs. 20.68 and 20.69) shows nodules of clear cells, compact cells, or a mixture of both.

Differential Diagnosis

♦ Adrenal cortical adenoma

Adrenal Cortical Hyperplasia Associated with Hyperaldosteronism

Clinical

♦ Approximately 40% of cases of primary hyperaldosteronism are due to adrenal cortical hyperplasia. Manifestations of hyperaldosteronism include hypertension, weakness, hypokalemia, and hypernatremia.

Macroscopic

♦ The cortex may be diffusely widened or have nodular appearance.

Microscopic

♦ Microscopically, the cortex is expanded by hyperplasia of zona glomerulosa, and tongues of glomerulosa cells often extend down into adjacent zona fasciculata. Patients treated with diuretic spironolactone (Aldactone) may have laminated eosinophilic inclusions (“spironolactone bodies”) in the cells.

Differential Diagnosis

♦ Adrenal cortical hyperplasia is associated with increased glucocorticoid levels. The hyperplastic cortex is made up mostly of fasciculata cells, rather than glomerulosa cells.

Adrenal Cortical Macronodular Hyperplasia

Clinical

♦ Macronodular hyperplasia is a rare type of primary adrenal hyperplasia with tumor-like enlargement of both glands. Patients usually present around 50 years of age with symptoms of hypercortisolism.

Macroscopic (Fig. 20.68)

♦ The adrenal glands are markedly enlarged (combined weight of 60–180 g), and grossly distorted by multiple nodules up to 3.5 cm in size. On cut section, the nodules are nonencapsulated and bright yellow in color.

Fig. 20.66. Adrenal cortical hyperplasia: Generally thickened yellow-brown cortex in cortical hyperplasia. The glands together weighed 25.2 g.

Fig. 20.67. Adrenal cortical hyperplasia: Irregular thickening with beginning nodularity of the cortex in diffuse cortical hyperplasia (Cushing syndrome).

Fig. 20.68. Cortical macronodular hyperplasia: Bilateral macronodular cortical hyperplasia featuring massive nodular enlargement of both adrenal glands. Total weight equals 218 g.
Microscopic (Fig. 20.69)
♦ The cortical cells are varied in appearance, predominantly large and vacuolated (lipid-laden) with some scattered, eosinophilic, compact (lipid-depleted) cells, and rare balloon cells. Pseudoglandular formations and focal lipomatous or myelolipomatous metaplasia can be seen.

Differential Diagnosis
♦ Adrenal cortical carcinoma
  − Adrenal cortical carcinomas are unilateral, typically weigh >100 g, show cellular atypia, mitoses, necrosis, and invasion
♦ Typical adrenal hyperplasia
  − In typical adrenal hyperplasia, the combined weight of adrenals is usually <50 g. The glands may appear nodular, but individual nodules are small (<0.5 cm)

Microadenomatous Hyperplasia (Primary Pigmented Nodular Adrenocortical Disease, PPNAD)

Clinical
♦ PPNAD is a type of primary adrenal hyperplasia with characteristic macroscopic findings. Patients are often young women with typical signs and symptoms of hypercortisolism (truncal obesity, muscle weakness, hypertension, abdominal striae, menstrual abnormalities/impotence). Osteoporosis is often a prominent feature
♦ PPNAD can occur in a familial setting with Carney syndrome with myxomas (cardiac, cutaneous, and mammary), spotty cutaneous pigmentation (ephelides, lentigines, and blue nevi), endocrine overactivity (acromegaly due to pituitary adenoma and sexual precocity due to large-cell calcifying Sertoli cell tumor of testes), and schwannomas (psammomatous melanotic type)

Macroscopic (Fig. 20.70)
♦ Multiple pigmented cortical nodules (1–3 mm in size) are situated in an atrophic cortex, often at the corticomedullary junction. The adrenal glands are of usually normal size

Fig. 20.69: Cortical macronodular hyperplasia: Low power micrograph showing adjacent large cortical nodules, which blend with a thickened cortex.

Fig. 20.70: Primary pigmented nodular adrenocortical disease. Slices of formalin-fixed right and left adrenal glands show multiple small brown and black nodules.

Fig. 20.71: Primary pigmented nodular adrenocortical disease. A nodule composed of cells with eosinophilic and clear cytoplasm straddles the corticomedullary function. The extranodular cortex is atrophic.

Microscopic (Fig. 20.71)
♦ The small nodules are composed of large granular eosinophilic cells, some with large hyperchromatic nuclei and prominent nucleoli. The cells contain lipofuscin pigment

Differential Diagnosis
♦ Pigmented cortical adenoma
  − Pigmented adrenal adenomas are larger (3–6 cm) than the nodules of PPNAD and are single
♦ Adrenal cortical carcinoma
  − Adrenal cortical carcinomas are single, dominant masses, rather than multiple nodules. Carcinomas show cellular atypia, mitoses, necrosis, fibrous bands, and invasion

Ovarian Thecal Metaplasia

Clinical
♦ Ovarian thecal metaplasia occurs in <5% of females, usually postmenopausal, and can rarely occur in males. It is of no known clinical significance
Endocrine Pathology

Macroscopic

Ovarian thecal metaplasia appears as a small (<2 mm) firm fibrous nodule, usually wedge-shaped, attached to adrenal capsule. Occasionally, multiple foci may be present.

Microscopic (Figs. 20.72 and 20.73)

Histologically, ovarian thecal metaplasia is a subcapsular proliferation of spindle cells that resemble normal ovarian stroma. Scattered cortical cells may be entrapped in the spindle cell proliferation. Fibrosis is common, and calcifications may be present.

Adrenal Medullary Hyperplasia

Clinical

Adrenal medullary hyperplasia is an uncommon hyperplastic expansion of the medulla. It is usually identified incidentally in association with MEN types 2A and 2B, but can occur sporadically on rare occasion. Adrenal medullary hyperplasia is thought to be precursor lesion to pheochromocytoma, especially in patients with MEN.

Macrosopic

Grossly, adrenal medullary hyperplasia shows an increase in adrenal medullary volume, which may be uniform or nodular and have a pearly gray color. Medullary tissue may extend beyond its normal location (restricted to head and body of adrenal) and be found withinalar and tail regions of the adrenal gland.

Microscopic (Fig. 20.75)

Microscopically, increased numbers of medullary cells are identified, either in sheets or nodules, expanding the medulla. The cells may show significant pleomorphism.

Differential Diagnosis

Adrenal cortical atrophy

- Adrenal cortical atrophy can mimic medullary hyperplasia grossly by making medulla appear relatively large compared with thin, attenuated cortex

Pheochromocytoma

- Nodular adrenal medullary hyperplasia may look similar to early pheochromocytoma and is thought to be a possible precursor of pheochromocytoma.

Fig. 20.72. Ovarian thecal metaplasia. A dense fibrous proliferation emanating from the adrenal capsule penetrates into the cortex.

Fig. 20.73. Ovarian thecal metaplasia: Clusters of cortical cells with clear cytoplasm are surrounded by a cellular spindle cell proliferation.

Fig. 20.74. Adrenal medullary hyperplasia: Slices of both adrenal glands show that the medulla of both glands is massively expanded and dwarfs the cortex.

Fig. 20.75. Adrenal medullary hyperplasia: Diffuse enlargement of the medulla without nodules.
Adrenal Cortical Adenoma

Clinical
- Adrenal cortical adenomas are benign cortical neoplasms, often associated with hormonal secretion. The signs and symptoms related to specific hormones elaborated by adenoma: hypercortisolism (Cushing syndrome), hyperaldosteronism (Conn syndrome), or increased androgenic or estrogenic steroids (adrenogenital syndrome). Some adenomas secrete multiple hormones and others are nonfunctional.
- Adrenal cortical adenomas are often identified incidentally on MRI or CT (“incidentalomas”), and autopsy series show 10–20% incidence.

Macroscopic
- Grossly, adrenal cortical adenomas are well-circumscribed, encapsulated masses, which are well-demarcated from surrounding cortex. The size varies from several grams up to 500 g in rare cases. Adrenal cortical tumors >100 g should be carefully evaluated for the presence of diagnostic features of malignancy. Although adrenal adenomas may show cystic degeneration, the presence of necrosis would be a worrisome feature for adrenal cortical carcinoma.
- In cortisol-secreting tumors, the adjacent cortex and contralateral adrenal gland are often atrophic due to suppression of pituitary ACTH secretion by the tumor’s hormone secretion.

Microscopic
- Adrenal adenomas are well-circumscribed, usually encapsulated, tumors composed of nests and cords of cells resembling those normally found in glomerulosa, fasciculata, or reticularis. Adenomas may be composed of a mixture of cell types. Some adenomas may show significant nuclear pleomorphism, which is thought to be degenerative.

Immunohistochemistry
- Adrenal cortical adenomas are positive for keratin (weak), Melan-A/Mart-1, inhibin, and synaptophysin and are negative for chromogranin and S-100.

Variants
- Adenomas associated with Cushing syndrome (Figs. 20.76–20.79)
  - Adrenal adenomas associated with Cushing syndrome usually measure 3–4 cm in diameter and weigh 10–50 g. They usually appear as mixture of colors (yellow to brown) and may occasionally be darkly pigmented (“black adenoma”). The constituent cells resemble zona reticularis and fasciculata with lipid-depleted (dark) and lipid-rich (pale) cytoplasm. Fatty or myeloid metaplasia is common. The cells of “black adenoma” contain abundant lipofuscin. The adjacent cortex (and that of contralateral adrenal) typically appears atrophic, with absence of normal zona reticularis.
- Adenomas associated with Conn syndrome (Figs. 20.80–20.83)
  - Adrenal adenomas associated with Conn syndrome are usually small (<2 cm), bright yellow, and often poorly demarcated from the surrounding cortex. The tumor cells resemble those of glomerulosa or fasciculata (clear cells) or a combination. In patients treated with diuretic spironolactone (Aldactone), tumor cells (and sometimes extratumoral zona glomerulosa cells) may contain eosinophilic inclusions (“spironolactone bodies”).
- Adenomas associated with adrenogenital syndromes...
Adenomas associated with adrenogenital syndromes tend to be larger, may have red-brown appearance, and are not associated with atrophy of the normal cortical tissue.

Fig. 20.78. Cortisol-secreting adenoma showing cells with clear and dark cytoplasm and foci of myeloid metaplasia.

Fig. 20.79. Cortical atrophy in association with cortisol-secreting adenoma. The thin extratumoral cortex has lost normal zonation and is largely composed of large cells with clear cytoplasm.

Fig. 20.80. Aldosterone-secreting adenoma: Yellow-orange tumor and associated cortex (showing outer zona fasciculata and inner zona reticularis) and medulla. The adrenal gland weighed 5.5 g.

Fig. 20.81. Aldosterone-secreting adenoma: The tumor is almost entirely composed of cells with clear cytoplasm. The attached cortex and medulla are normal.

Fig. 20.82. Aldosterone-secreting adenoma: The tumor features large clear cells arranged in trabeculae supported by a minimal fibrovascular stroma. There is focal nucleomegaly.

Fig. 20.83. Spironolactone bodies: There are scattered laminated eosinophilic structures in a group of cells with eosinophilic cytoplasm (the latter unusual in an aldosterone-secreting adenoma).

- Adenomas associated with adrenogenital syndromes tend to be larger, may have red-brown appearance, and are not associated with atrophy of the normal cortical tissue.
These tumors are relatively uncommon and must be carefully distinguished from cortical carcinoma

♦ Nonfunctional adenomas and cortical nodules
  - Nonfunctional adenomas are small (>3 cm), yellow to brown in color, and may be multicentric. They are not associated with atrophy of normal cortical tissue

♦ Oncocytic adenoma (oncocytoma)
  - Oncocytic adenoma is an epithelial adrenal cortical neoplasm composed of oncocytic cells, which is often asymptomatic, but may be associated with hormonal syndrome. Oncocytomas are usually benign, but the behavior is difficult to predict with certainty
  - Grossly (Fig. 20.84), oncocytic adenomas can be variable in size (60–850 g), but are usually well-circumscribed and often encapsulated. They are typically tan-brown in color, often have a central scar, and may show hemorrhage or cystic change
  - Microscopically (Fig. 20.85), these tumors are composed of sheets of large regular polygonal cells with abundant granular eosinophilic cytoplasm, and often show some nuclear pleomorphism

**Differential Diagnosis**

♦ Nodular or macronodular hyperplasia
  - Nodular hyperplasia is characterized by multiple nodules rather than single dominant nodule. The adjacent cortex and contralateral adrenal gland appears hypertrophic, not atrophic

♦ Adrenal cortical carcinoma
  - Adrenal cortical carcinomas are typically large tumors (>100 g) and show nuclear atypia, mitoses, necrosis, and invasion

♦ Pheochromocytoma
  - Arising from adrenal medulla with normal adrenal cortex stretched out over its surface, pheochromocytomas are red-brown in color with areas of hemorrhage or cystic degeneration if large. Organoid growth pattern with nests of cells (“zellballen”) and delicate vascular septa are characteristic
  - Pheochromocytomas are immunoreactive for neurofilament, chromogranin, and synaptophysin, and negative for keratins, Melan-A/Mart-1, and inhibin. S-100 marks the sustentacular cells

**Adrenal Cortical Carcinoma**

**Clinical**

♦ Adrenal cortical carcinomas (ACC) are rare, accounting for about 3% of endocrine tumors. All ages can be affected, although some studies have found a higher incidence in the 40- to 50-year old population. Females are affected more commonly than males
  - Approximately 45–49% of tumors are functional with production of glucocorticoids resulting in Cushing syndrome or androgens with virilization. Hormonal hypersecretion is more common in women
  - Adrenal cortical carcinomas are aggressive tumors with 5-year survival of 25%. They are treated surgically with improved survival with localized disease that is completely removed surgically. Adjuvant therapies (op-DDE) have limited, if any, benefit

**Macroscopic (Fig. 20.86)**

♦ Adrenal cortical carcinomas vary in size, but are usually large cortical masses, usually >6 cm in size (usually >100 g in adults and >500 g in children). On cut section, ACCs are pink to tan to yellow, depending on lipid content of tumor cells, and often lobulated with areas of fibrosis, necrosis, hemorrhage, and invasion of adjacent structures

**Microscopic (Figs. 20.87–20.89)**

♦ Adrenal cortical carcinomas have a varied cellular appearance depending on lipid content: small cells with eosinophilic cytoplasm (lipid-depleted) to large and vacuolated (lipid-laden) cells. The growth pattern may be alveolar, trabecular, or diffuse
  - Histologic features of malignancy include invasive growth, angiolymphatic invasion, necrosis, broad fibrous bands, capsular invasion, increased mitotic rate (>5 per 50 high power

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![Fig. 20.84. Oncocytoma: Brown cut surface with some gaping vessels.](image1)

![Fig. 20.85. Oncocytoma: Moderately large cells with eosinophilic cytoplasm and nuclei are central and eccentric. Multinucleation is present.](image2)
atypical mitotic figures, prominent clear cells, and nuclear pleomorphism

Immunohistochemistry (Table 20.4)
- Adrenal cortical carcinomas are positive for low molecular weight keratin (CAM 5.2), and may show focal staining for other keratins and vimentin. They are also positive for Melan A/MART1 (A103), but are negative for S-100. Functioning tumors show positivity for inhibin. Adrenal cortical carcinomas are positive for synaptophysin, but they are negative for chromogranin, which is helpful in differentiating them from pheochromocytomas

Variants
- Oncocytic adrenal carcinoma
  - In a series of ACC from Mayo Clinic, 6 of 67 (11.2%) ACC were composed predominantly of oncocytic cells. These tumors ranged in size from 8 to 20 cm, and three of these patients died of disease. Only one of the oncocytic carcinomas (20 cm) was functional (feminizing)
- Myxoid adrenal cortical carcinoma
  - Adrenal cortical carcinomas and adenomas can show prominent myxoid change and must be distinguished from metastases to the adrenal glands
- Pediatric adrenal cortical carcinoma
  - Differentiating ACC from adenoma in children is very difficult. Pediatric ACC can occur in Beckwith–Wiedemann syndrome, but most occur sporadically. Patients often present with hormone-related symptoms. Features associated with malignant clinical behavior are tumor weight >400 g, size >10.5 cm, vena cava invasion, capsular and/or vascular invasion, extension into periadrenal soft tissue, confluent necrosis, severe nuclear atypia, >15 mitotic figures/20 hpf, and atypical mitotic figures

Differential Diagnosis (Table 20.4)
- Adrenal cortical adenoma
  - Adrenal cortical adenomas are usually smaller (usually 3–6 cm) than ACC and well-circumscribed, often encapsulated.
Adrenal adenomas may show some nuclear pleomorphism, but generally lack necrosis, increased mitotic activity, and invasion of capsule or vessels.

**Metastatic tumors to the adrenal gland**
- Adrenal cortical carcinomas must be differentiated from metastatic carcinomas such as from lung, breast, gastrointestinal tract, thyroid, and kidney. The growth pattern of metastases is usually solid rather than alveolar or trabecular. Immunohistochemical studies are very helpful in difficult cases. Metastatic lung adenocarcinomas show strong diffuse immunopositivity for cytokeratin 7 and TTF-1. Metastatic breast cancer is positive for cytokeratin 7, GCDFP-15 (BRST-2), mammoglobin, estrogen, and progesterone receptors, and is negative for TTF-1 and Melan A/MART-1.
- Metastatic melanomas are positive for cytokeratin 20 and CDX2, markers generally negative in ACC.

**Melanoma**
- Although exceptionally rare cases of primary adrenal melanomas have been described, the overwhelming majority of melanomas involving the adrenal gland are metastatic. Malignant melanomas often show melanin pigment and are positive for Melan A/Mart-1, similar to adrenal cortical tumors, but melanomas are usually positive for other markers of melanocytic differentiation such as S-100, tyrosinase, and HMB45, which are negative in adrenal cortical tumors.

### Table 20.4. Immunophenotype of Differential Diagnosis of Adrenal Cortical Carcinoma

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Keratin</th>
<th>Chromogranin</th>
<th>Synaptophysin</th>
<th>TTF</th>
<th>S-100</th>
<th>MelanA/Mart1</th>
<th>Inhibin</th>
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<tr>
<td>Adrenal cortical carcinoma</td>
<td>+ (CAM 5.2)</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Metastatic lung</td>
<td>+ (keratin 7)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Metastatic melanoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

*S-100 protein marks sustentacular cells

**Pheochromocytoma**

**Clinical**
- Pheochromocytomas are composed of adrenal medullary chromaffin cells. The highest incidence of pheochromocytoma is in fourth and fifth decades, although 10% occur in children. Patients present with signs and symptoms of catecholamine secretion (hypertension, cardiac dysrhythmias, and diaphoresis). Ectopic hormones may be produced as well (ACTH, somatostatin, or calcitonin). Extraadrenal pheochromocytomas (paragangliomas) account for approximately 10–20% of cases and occur elsewhere in retroperitoneum, mediastinum, neck, or bladder. Ten to twenty percent of pheochromocytomas are associated with familial syndromes: MEN Type 2A and 2B, von Hippel-Lindau disease, von Recklinghausen disease, and Sturge–Weber syndrome.
- Approximately 5–10% of pheochromocytomas are malignant. There are no reliable gross or histologic criteria exist for malignancy other than invasion of adjacent structures or metastases.

**Macroscopic (Fig. 20.90)**
- Pheochromocytoma usually presents as an encapsulated mass, 3–5 cm, weighing <100, gray-pink to tan-brown in color. The tumors usually have a soft consistency and may have areas of hemorrhage and cyst formation in larger tumors.

**Microscopic (Fig. 20.91)**
- Pheochromocytomas grow in cords or nests (zell-ballen = “cell balls”), with delicate fibrovascular septa. The cells are variable in size with generally basophilic granular cytoplasm that may be vacuolated in some cases. Occasional spindled cells can be seen as well as PAS+ cytoplasmic hyaline globules. Cytologically, the cells are round to oval with slightly irregular nuclei, coarsely clumped chromatin (salt and pepper chromatin) and single, ordinarily inconspicuous nucleoli. Moderate nuclear pleomorphism may be present. Mitoses can be seen, but are not prominent.
Immunohistochemistry
- Tumor cells are immunoreactive for chromogranin and synaptophysin with S-100 staining thin, spindled sustentacular cells (Table 20.4). They are negative for cytokeratins

Differential Diagnosis
- Adrenal cortical adenoma
  - Adrenal cortical adenomas are small (3–6 cm) with bright yellow to tan-brown color and uninvolved adrenal cortical tissue usually appears atrophic. Adrenal cortical adenomas are positive for synaptophysin, but negative for chromogranin. Adrenal cortical tumors also show weak immunopositivity for keratin while pheochromocytomas are negative

- Adrenal cortical carcinoma
  - Adrenal cortical carcinomas often show marked nuclear pleomorphism, necrosis, invasion, and prominent mitotic activity. Adrenal cortical carcinomas are positive for synaptophysin, but negative for chromogranin. Adrenal cortical tumors also show weak immunopositivity for keratin while pheochromocytomas are negative

- Metastatic carcinoma
  - Common primary sites of metastases to the adrenal include lung, breast, gastrointestinal tract, thyroid, and kidney. The growth pattern of metastases to the adrenal is usually solid rather than nested or zell-ballen. Metastatic carcinomas are positive for keratin, and may be positive for other markers characteristic of the location of the primary such as TTF-1 in pulmonary adenocarcinoma, etc

- Melanoma
  - Although exceptionally rare cases of melanoma may be primary in the adrenal gland, the absolute overwhelming majority of melanoma in the adrenal gland is metastatic. Melanomas often show melanin pigment, and immunohistochemically mark for S-100, Melan A/MART1, and HMB-45

Myelolipoma
Clinical
- Myelolipoma is a benign mixed stromal tumor composed of mature adipose and myeloid elements. Myelolipoma is usually an incidental finding at autopsy or adrenalectomy. Small foci of myelolipomatous change are commonly seen in adenomas or hyperplasias

Macroscopic (Fig. 20.92)
- Myelolipomas are small, nonencapsulated spongy lesions, often bright yellow with scattered small red-brown foci

Microscopic (Fig. 20.93)
- These tumors are composed of mature adipose tissue with scattered normal-appearing hematopoietic elements

Ganglioneuroma
Clinical
- Ganglioneuroma is a benign neurogenic tumor arising in adrenal medulla and sympathetic ganglia, which occur most often in older children (>7 years) and young adults. These tumors may present as a mass or be seen as an incidental finding on CT or MRI or at autopsy. Ganglioneuromas may be associated with clinical syndromes such as hypertension, diarrhea, and/or hypokalemia (95% of patients have detectable elevations in catecholamine metabolites in urine). These tumors may be solitary or associated with other neurogenic tumors. Less than 30% of cases located in adrenal glands as most found in posterior mediastinum or in retroperitoneum, particularly presacral region
Myelolipomas are large (average size = 8 cm), sharply circumscribed firm masses, homogenous gray-white in appearance.

**Microscopic (Figs. 20.94 and 20.95)**

- The stroma closely resembles neurofibroma, with thin wavy spindled cells (Schwann cells) in collagenous matrix. Scattered mildly atypical to normal ganglion cells with abundant cytoplasm and multiple nuclei are seen. These tumors may contain lymphocytic infiltrates that may be confused with neuroblasts.

**Immunohistochemistry**

- Stroma is immunoreactive with S-100 protein (Table 20.4). Ganglion cells are immunoreactive with neurofilament, chromogranin, and neuron-specific enolase.

**Differential Diagnosis**

- **Neurofibroma**
  - The stroma in neurofibroma may appear identical to that of ganglioneuroma; however, no ganglion cells are seen in neurofibroma.

- **Ganglioneuroblastoma**
  - Ganglioneuroblastoma contains less differentiated foci of neuroblasts (with typical microscopic and immunohistochemical features).

**Ganglioneuroblastoma**

**Clinical**

- Ganglioneuroblastoma is a combination tumor representing maturational intermediate between neuroblastoma and ganglioneuroma, which is usually seen in children <10 years, can occur in adults. This tumor usually presents as intraabdominal or intrathoracic mass, rarely seen with hormonal syndromes similar to neuroblastoma. These tumors may occur in the adrenal gland, but are more in extra-adrenal retroperitoneum and mediastinum.
**Macroscopic**

- The histologic features are varied, depending on relative proportion of fully differentiated and undifferentiated (or differentiating) elements. Differentiated variants tend to resemble typical ganglioneuromas (circumscribed firm white-gray masses). Undifferentiated variants show large nodular areas grossly resembling neuroblastoma (soft white-gray with areas of necrosis and hemorrhage).

**Microscopic**

- Differentiated and undifferentiated areas with morphologic features of ganglioneuroma and neuroblastoma are seen, respectively. Differentiated areas have collagenous stroma with scattered atypical ganglion cells, while undifferentiated areas show sheets or nodules of small regular cells with hyperchromatic nuclei.

**Immunohistochemistry**

- Immunohistochemical features are characteristic for respective elements (see neuroblastoma and ganglioneuroma).

**Neuroblastoma**

**Clinical**

- Neuroblastoma is a malignant neurogenic tumor composed of immature neuroblasts occurring in 1 in 7,000–10,000 live births. Fifty percent of patients are <2-years old, 90% <8-years old; median age = 21 months. Patients usually present with intraabdominal mass, and these tumors may rarely be associated with hormonal (catecholamines, vasoactive intestinal peptide) or other para-neoplastic syndromes. Seven percent occur in retroperitoneum, usually adrenal gland. Other sites include mediastinum, head and neck region, and pelvic region.

- Prognosis related to number of factors including stage, age, favorable or unfavorable histology, ploidy, N-myc, adrenal or extra-adrenal location, among others.

- Common cytogenetic abnormalities include 1p deletions and amplification of N-myc oncogene. There is an association with Beckwith–Wiedemann syndrome and neurofibromatosis.

**Macroscopic (Fig. 20.96)**

- Neuroblastomas are usually solitary, soft gray, well-circumscribed masses, which may contain areas of hemorrhage, necrosis, calcification, or cystic degeneration.

**Microscopic (Fig. 20.97)**

- The individual cells are separated by a fine fibrillar eosinophilic matrix. The cells are small and uniform, with little cytoplasm and round, hyperchromatic nuclei with small nucleoli. The cells are arranged in sheets, which form vague lobules divided by thin fibrovascular septa, and Homer–Wright pseudorosettes (rings of neuroblasts, 1–2 layers thick, surrounding central area filled with eosinophilic fibrillary material) are seen in 30% of cases. Necrosis, hemorrhage, and calcifications are common findings.

- Tumors may show varying degrees of differentiation toward ganglioneuroma, with cellular and nuclear enlargement, prominent nucleoli, and stroma resembling neurofibroma.

**Immunohistochemistry**

- The tumor cells are immunoreactive for neuron-specific enolase, chromogranin, synaptophysin, microtubule-associated proteins, neurofilaments, alpha-internexin, secretogranin II, and vasoactive intestinal peptide. Stromal cells immunoreactive for S-100 protein, glial fibrillary acidic protein, and myelin basic protein.

**Differential Diagnosis**

- Ewings sarcoma (extraskeletal)
  - Ewing sarcoma/PNET usually affects older patients (>5 years). The histology is very similar to neuroblastoma (may even have pseudorosettes rarely). Cytogenetic studies show a characteristic t(11;22) translocation.

- Nephroblastoma (Wilm tumor)
Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastases
- N1: Regional lymph node metastases
  - N1a: Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
  - N1b: Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)

Distant Metastasis (M)

- M0: No distant metastasis
- M1: Distant metastasis

TNM CLASSIFICATION OF THYROID CARCINOMAS (2010 REVISION)

Primary Tumor (T)*

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Tumor 2 cm in greatest dimension limited to thyroid
- T1a: Tumor 1 cm or less, limited to the thyroid
- T1b: Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
- T2: Tumor more than 2 cm but not more than 4 cm in greatest dimension, limited to thyroid
- T3: Tumor more than 4 cm in greatest dimension limited to thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissue)
- T4a: Moderately advanced disease; tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
- T4b: Very advanced disease; tumor invades prevertebral fascia or encase carotid artery or mediastinal vessels

*All anaplastic carcinomas are considered T4, which is subdivided into T4a (intrathyroid anaplastic carcinoma) and T4b (extrathyroidal anaplastic carcinoma)

Regional Lymph Nodes (N)

- N0: No regional lymph node metastases
- N1: Regional lymph node metastases
  - N1a: Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)

SUGGESTED READING

Thyroid


Endocrine Pathology

20-49


Parathyroid


Adrenal


Essentials of Anatomic Pathology
Cheng, L.; Bostwick, D.G. (Eds.)
2011, XV, 1879 p. 2165 illus., 2013 illus. in color., Hardcover