Pathology of endocrine

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Parathyroid Glands

The parathyroid glands are derived developmentally from pharyngeal pouches that also give rise to the thymus.

They are most commonly located in close proximity to the upper and lower poles of each thyroid lobe .

The four parathyroid glands are composed of two cell types: chief cells and oxyphil cells. Chief cells predominate. Chief cells have secretory granules containing parathyroid hormone (PTH).

The function of the parathyroid glands is to regulate calcium homeostasis. The activity of the parathyroid glands is controlled by the level of free (ionized) calcium in the blood. Normally, decreased levels of free calcium stimulate the synthesis and secretion of PTH. Several metabolic functions of PTH regulate serum calcium levels:

- *Increased renal tubular reabsorption of calcium, thereby conserving free calcium*
- *Increased conversion of vitamin D to its active dihydroxy form in the kidneys, which, in turn, augments gastrointestinal calcium absorption*
- *Increased urinary phosphate excretion, thereby lowering serum phosphate levels and further increasing calcium (since phosphate binds to ionized calcium)*
- *Enhanced osteoclastic activity (i.e., bone resorption, thus releasing ionized calcium), by promoting the differentiation of osteoclast progenitor cells into mature osteoclasts*

HYPERPARATHYROIDISM

Hyperparathyroidism is caused by elevated PTH and is classified into primary, secondary, and tertiary types.

- ***Primary hyperparathyroidism:*** *an autonomous overproduction of PTH, usually resulting from an adenoma or hyperplasia of parathyroid tissue*
- ***Secondary hyperparathyroidism:*** *compensatory hypersecretion of PTH in response to prolonged hypocalcemia, most commonly from chronic renal failure*
- ***Tertiary hyperparathyroidism:*** *persistent hypersecretion of PTH, even after the cause of prolonged hypocalcemia is corrected (e.g., after renal transplant)*

Primary Hyperparathyroidism

Primary hyperparathyroidism is one of the most common endocrine disorders, and it is an important cause of hypercalcemia. The frequency of the various parathyroid lesions underlying hyperfunction is as follows:

- *Adenoma: 85% to 95%*
- *Primary hyperplasia (diffuse or nodular): 5% to 10%*
- *Parathyroid carcinoma: ~1%*

The most common cause of primary hyperparathyroidism is a solitary sporadic parathyroid adenoma

MORPHOLOGY

The morphologic changes seen in primary hyperparathyroidism involve the parathyroid glands and organs that are affected by elevated levels of PTH and calcium. Parathyroid adenomas are almost always solitary and, like normal parathyroid glands, may be in close proximity to the thyroid or in an ectopic site (e.g., the mediastinum). The typical adenoma averages 0.5 to 5 g and consists of a well-circumscribed, soft, tan to reddish-brown nodule invested by a delicate capsule. In contrast to primary hyperplasia, the glands outside the adenoma are usually normal in size or shrunken because of feedback inhibition by elevated levels of serum calcium. Microscopically, parathyroid adenomas are mostly composed of uniform, polygonal chief cells with small, centrally placed nuclei . At least a few nests of larger oxyphil cells are present as well; uncommonly, adenomas are composed entirely of this cell type (oxyphil adenomas).

These may resemble Hürthle cell tumors in the thyroid. A rim of compressed, nonneoplastic parathyroid tissue, generally separated by a fibrous capsule, is often visible at the edge of the adenoma. Mitotic figures are rare, but it is not uncommon to find bizarre and pleomorphic nuclei even within adenomas (so-called endocrine atypia); this is not a criterion for malignancy. In contrast to the normal parathyroid parenchyma, adipose tissue is inconspicuous. Primary hyperplasia may occur sporadically or as a component of MEN syndrome. Although classically all four glands are involved, there is frequently asymmetry with apparent sparing of one or two glands, making the distinction between hyperplasia and adenoma difficult. The combined weight of all glands rarely exceeds 1 g and is often less.

Microscopically, *the most common pattern seen is that of chief cell hyperplasia, which may involve the glands in a diffuse or multinodular pattern. Less commonly, the constituent cells contain abundant glycogen, giving them a clear appearance in histologic sections ("water-clear cell hyperplasia"). In many instances, there are islands of oxyphils, and poorly developed, delicate fibrous strands may envelop the nodules. As in the case of adenomas, stromal fat is inconspicuous within hyperplastic glands*

Parathyroid carcinomas may be circumscribed lesions that are difficult to distinguish from adenomas, or they may be clearly invasive neoplasms. These tumors enlarge one parathyroid gland and consist of gray-white, irregular masses that sometimes exceed 10 g in weight. The cells are usually uniform and resemble normal parathyroid cells, and are arrayed in nodular or trabecular patterns. The mass is usually enclosed by a dense, fibrous capsule. Diagnosis of carcinoma based on cytologic detail is unreliable, and invasion of surrounding tissues and metastasis are the only reliable criteria.

Clinical Features

• Asymptomatic hyperparathyroidism. Because serum calcium levels are routinely assessed.

Symptomatic primary hyperparathyroidism. The signs and symptoms of hyperparathyroidism reflect the combined effects of increased PTH secretion and hypercalcemia. symptoms includes the following:

• Bone disease and bone pain secondary to fractures of bones weakened by osteoporosis or osteitis fibrosa cystica

• Nephrolithiasis (renal stones) in 20% of newly diagnosed patients, with attendant pain and obstructive uropathy.

Chronic renal insufficiency and abnormalities in renal function lead to polyuria and secondary polydipsia.

• Gastrointestinal disturbances, including constipation, nausea, peptic ulcers, pancreatitis, and gallstones

- *Central nervous system alterations, including depression, lethargy, and eventually seizures*
- *Neuromuscular abnormalities, including weakness and fatigue*
- *Cardiac manifestations, including aortic or mitral valve calcifications (or both)*

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is caused by any condition that gives rise to chronic hypocalcemia, which, in turn, leads to compensatory overactivity of the parathyroid glands. Renal failure is by far the most common cause of secondary hyperparathyroidism although several other diseases, including inadequate dietary intake of calcium, steatorrhea, and vitamin D deficiency, may also cause this disorder.

MORPHOLOGY

The parathyroid glands in secondary hyperparathyroidism are hyperplastic. As in primary hyperparathyroidism, the degree of glandular enlargement may be asymmetric. Microscopically, the hyperplastic glands contain an increased number of chief cells, or water-clear cells in a diffuse or multinodular distribution. Fat cells are decreased in number. Metastatic calcification may be seen in many tissues, including the lungs, heart, stomach, and blood vessels.

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Clinical Features

The clinical features of secondary hyperparathyroidism are usually dominated by the inciting chronic renal failure.

Secondary hyperparathyroidism is usually not as severe or as prolonged as primary hyperparathyroidism, In a minority of patients, parathyroid activity may become autonomous and excessive, with resultant hypercalcemia, a process termed tertiary hyperparathyroidism. Parathyroidectomy may be necessary to control the hyperparathyroidism in such patients.

HYPOPARATHYROIDISM

Hypoparathyroidism is far less common than is hyperparathyroidism.

- *Surgically induced hypoparathyroidism*
- *Autoimmune hypoparathyroidism*
- *Autosomal-dominant hypoparathyroidism : caused by gain-of-function mutations in the calcium-sensing receptor (CASR) gene.*
- *Familial isolated hypoparathyroidism (FIH)*
- *Congenital absence*

Clinical Features

The major manifestations of hypoparathyroidism are related to the severity and chronicity of the hypocalcemia.

- *The hallmark of hypocalcemia is tetany, which is characterized by neuromuscular irritability, resulting from decreased serum calcium levels. The symptoms range from circumoral numbness or paresthesias (tingling) of the distal extremities and carpopedal spasm, to life threatening laryngospasm and generalized seizures.*
- *Mental status changes include emotional instability, anxiety and depression, confusional states, hallucinations, and frank psychosis.*
- *Intracranial manifestations .*
- *Ocular disease*
- *Cardiovascular manifestations include a conduction defect that produces a characteristic prolongation of the QT interval in the electrocardiogram.*
- *Dental abnormalities.*

Pituitary Gland

The anterior pituitary, or adenohypophysis, which constitutes about 80% of the gland, produces trophic hormones that stimulate the production of hormones from the thyroid, adrenal, and other glands.

CLINICAL MANIFESTATIONS OF PITUITARY DISEASE

The manifestations of pituitary disorders are related to either excess or deficiency of pituitary hormones, or to mass effects.

Hyperpituitarism arises from excess secretion of trophic hormones. The causes of hyperpituitarism include hyperplasias, adenomas, and carcinomas of the anterior Pituitary.

Hypopituitarism results from deficiency of trophic hormones. It may be caused by ischemic injury, surgery or radiation, inflammatory disorders, and the mass effects of nonfunctional pituitary adenomas. Symptoms related to local mass effects. Because of the close proximity of the optic nerves and chiasm to the sella, visual fields.
Diseases of the posterior pituitary often come to clinical attention because of increased or decreased secretion of ADH and associated changes in fluid and electrolyte balances.

PITUITARY ADENOMAS AND HYPERPITUITARISM

The most common cause of hyperpituitarism is an adenoma arising in the anterior lobe. Pituitary adenomas are classified on the basis of the hormones and cell type–specific transcription factors that are expressed by the tumor cells . Some pituitary adenomas secrete two hormones (GH and prolactin being the most common combination), and rarely, pituitary adenomas are plurihormonal. Less common causes of hyperpituitarism include pituitary carcinomas and some hypothalamic disorders. By contrast, large pituitary adenomas, and particularly nonfunctioning ones, may cause hypopituitarism by destroying the adjacent normal anterior pituitary parenchyma.

Pituitary adenomas are usually found in adults; the peak incidence is from 35 to 60 years of age. They are designated, somewhat arbitrarily, microadenomas if they are less than 1 cm in diameter and macroadenomas if they exceed 1 cm in diameter. Nonfunctional adenomas are likely to come to clinical attention at a later stage than those associated with endocrine abnormalities and are therefore more likely to be macroadenomas. Based on autopsy studies, the prevalence of pituitary adenomas in the population is estimated to be about 14%, but the vast majority of these lesions are clinically silent microadenomas ("pituitary incidentaloma").

MORPHOLOGY

The typical pituitary adenoma is soft and well-circumscribed. Small adenomas may be confined to the sella turcica, but with expansion they frequently erode the sella turcica and anterior clinoid processes. Larger lesions may extend superiorly through the diaphragm sella into the suprasellar region, compressing the optic chiasm and adjacent structures, such as cranial nerves . In as many as 30% of cases, the adenomas are not encapsulated and infiltrate neighboring tissues such as the cavernous and sphenoid sinuses, dura, and on occasion, the brain itself. Such lesions are termed aggressive adenomas. Not unexpectedly, macroadenomas are more likely to be invasive and to have foci of hemorrhage and necrosis.

Histologically, *typical pituitary adenomas are composed of uniform (monomorphic), polygonal cells arrayed in sheets or cords.*

The supporting connective tissue, or reticulin, is sparse, accounting for the soft, gelatinous consistency of many of these tumors. This cellular monomorphism and the absence of a significant reticulin network distinguish pituitary adenomas from normal anterior pituitary parenchyma . Immunohistochemical stains for hormones and lineage-specific transcription factors are used to identify specific pituitary adenoma subtypes. Mitotic activity and expression of Ki-67 (MIB-1, a marker of cycling cells) are typically low in pituitary adenomas; higher-than-normal rates of cell division are associated with more aggressive tumors

Table 24.1 Classification of Pituitary Adenomas

Adenoma Type	Hormone	Transcription Factor	Morphologic Variant	Associated Syndrome[a]
Somatotroph adenoma	GH	PIT-1	Densely granulated adenoma	Gigantism (children)
	GH	PIT-1	Sparsely granulated adenoma	Acromegaly (adults)
	GH, PRL (in same cells)	PIT-1, ERα	Mammosomatotroph adenoma	
	GH, PRL (in different cells)	PIT-1, ERα	Mixed somatotroph-lactotroph adenoma	
Lactotroph adenoma	PRL	PIT-1, ERα	Sparsely granulated adenoma	Galactorrhea and amenorrhea (in females)
	PRL	PIT-1, ERα	Densely granulated adenoma	
	PRL, GH (focal and variable)	PIT-1, ERα	Acidophilic stem cell adenoma	Sexual dysfunction, infertility
Thyrotroph adenoma	TSH	PIT-1	Thyrotroph adenoma	Hyperthyroidism
Corticotroph adenoma	ACTH	TPIT	Densely granulated adenoma	Cushing syndrome
	ACTH	TPIT	Sparsely granulated adenoma	Nelson syndrome
	ACTH	TPIT	Crooke cell adenoma (prominent intracytoplasmic cytokeratin filaments)	Mass effects (20% of corticotroph adenomas are hormonally silent)
Gonadotroph adenoma	FSH, LH	SF-1, GATA-2, ERα	Gonadotroph adenoma	Mass effects and hypopituitarism (most gonadotroph adenomas are hormonally silent)
Null cell adenoma	None	None		Mass effects
Plurihormonal adenoma	GH, PRL, TSH	PIT-1		

HYPOPITUITARISM

Hypopituitarism refers to decreased secretion of pituitary hormones, which can result from diseases of the hypothalamus or of the pituitary. Hypofunction of the anterior pituitary occurs when approximately 75% of the parenchyma is lost or absent. When accompanied by evidence of posterior pituitary dysfunction in the form of diabetes insipidus, hypopituitarism is almost always of hypothalamic origin. Most cases of hypopituitarism arise from destructive processes involving the anterior pituitary, as follows:

- *Tumors and other mass lesions*
- *Traumatic brain injury and subarachnoid hemorrhage*
- *Pituitary surgery or radiation*
- *Pituitary apoplexy:this is caused by a sudden hemorrhage into the pituitary gland*
- *Ischemic necrosis of the pituitary (Sheehan syndrome), also known as postpartum necrosis, is the most common form of ischemic necrosis of the anterior pituitary. During pregnancy, the anterior pituitary enlarges to almost twice its normal size. This physiologic expansion of the gland is not accompanied by an increase in blood supply.*
- *Rathke cleft cyst:*
- *Empty sella syndrome:*
- *Hypothalamic lesions: hypothalamic lesions can also affect the pituitary by causing a deficiency of pituitary hormone–releasing factors.*
- *Inflammatory disorders and infections, such as sarcoidosis or tuberculous meningitis*
- *Genetic defects:*

The clinical manifestations of anterior pituitary hypofunction vary depending on the specific hormones that are lacking.

- *Children can develop growth failure (pituitary dwarfism) due to growth hormone deficiency.*
- *Gonadotropin (LH and FSH) deficiency leads to amenorrhea and infertility in women and decreased libido, impotence, and loss of pubic and axillary hair in men.*
- *TSH and ACTH deficiencies result in symptoms of hypothyroidism and hypoadrenalism, respectively.*
- *Prolactin deficiency results in failure of postpartum lactation.*
- *The anterior pituitary is also a rich source of melanotropins (also known as melanocyte-stimulating hormone), synthesized from the same precursor molecule that produces ACTH; therefore, one of the manifestations of hypopituitarism includes pallor due to a loss of stimulatory effects on melanocytes.*

HYPOTHALAMIC SUPRASELLAR TUMORS

Craniopharyngioma is thought to arise from vestigial remnants of Rathke pouch. These slow-growing tumors account for 1% to 5% of intracranial tumors. A small minority of these lesions occurs within the sella, but most are suprasellar, with or without intrasellar extension. A bimodal age distribution is observed, with one peak in childhood (5 to 15 years) and a second peak in adults 65 years of age or older.

Patients usually come to attention because of headaches and visual disturbances, while children sometimes present with growth retardation due to pituitary hypofunction and GH Deficiency .

MORPHOLOGY

Craniopharyngiomas average 3 to 4 cm in diameter; they may be encapsulated and solid, but more commonly they are cystic and sometimes multiloculated. They often encroach on the optic chiasm or cranial nerves, and not infrequently they bulge into the floor of the third ventricle and base of the brain. Two distinct histologic variants are recognized: adamantinomatous craniopharyngioma (most often observed in children) and papillary craniopharyngioma (most often observed in adults). The adamantinomatous type

Adrenal Cortex

Adrenocortical function is essential for the production of cortisol, aldosterone, and related hormones that manage stress, electrolyte balance, and blood pressure. Complete loss of adrenocortical function is rapidly fatal under conditions of severe stress (e.g., surgery, infection).

Adrenocortical Hyperfunction (Hyperadrenalism)

The syndromes of adrenal hyperfunction are caused by overproduction of the three major hormones of the adrenal cortex (1) Cushing syndrome, characterized by an excess of cortisol; (2) hyperaldosteronism as a result of excessive aldosterone; and (3) adrenogenital or virilizing syndromes caused by an excess of androgens.

Hypercortisolism (Cushing Syndrome)

Pathogenesis

This disorder is caused by conditions that produce elevated glucocorticoid levels. Cushing syndrome can be broadly divided into exogenous and endogenous causes. The vast majority of cases of Cushing syndrome are the result of the administration of exogenous glucocorticoids (iatrogenic Cushing syndrome). The endogenous causes can, in turn, be divided into those that are ACTH dependent and those that are ACTH independent . ACTH-secreting pituitary adenomas account for 60% to 70% of cases of endogenous hypercortisolism. The pituitary form of this syndrome is referred to as Cushing disease.

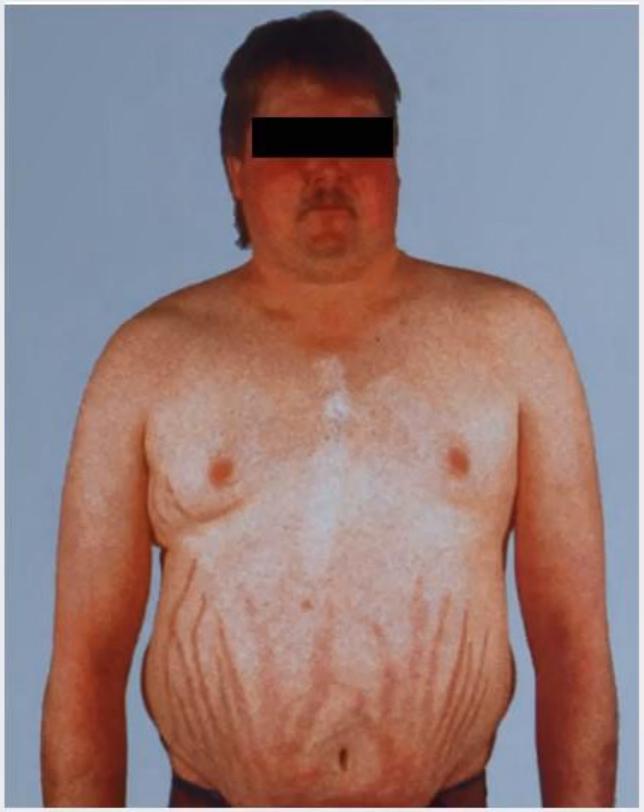
The disorder affects women about four times more frequently than men and occurs most frequently in young adults. In the vast majority of cases, it is caused by an ACTH-producing pituitary microadenoma. The adrenal glands in individuals with Cushing disease are characterized by variable degrees of nodular cortical hyperplasia caused by the elevated levels of ACTH. The cortical hyperplasia, in turn, is responsible for hypercortisolism.

Secretion of ectopic ACTH by nonpituitary tumors accounts for about 5% to 10% of ACTH-dependent Cushing syndrome cases.

Primary adrenal neoplasms, such as adrenal adenoma (~10% to 20%) and carcinoma (~5% to 7%) are the most common underlying causes of ACTH-independent Cushing syndrome.

Table 24.9 Clinical Features of Cushing Syndrome

Feature	Percent
Obesity or weight gain	95%[a]
Facial plethora	90%
Rounded face	90%
Decreased libido	90%
Thin skin	85%
Decrease in linear growth in children	70%–80%
Menstrual irregularity	80%
Hypertension	75%
Hirsutism	75%
Depression/emotional liability	70%
Easy bruising	65%
Glucose intolerance	60%
Weakness	60%
Osteopenia or fracture	50%
Nephrolithiasis	50%



Primary Hyperaldosteronism:

Hyperaldosteronism is the generic term for a group of closely related conditions characterized by chronic excess aldosterone secretion. Hyperaldosteronism may be primary, or it may be secondary to an extra-adrenal cause. Primary hyperaldosteronism stems from an autonomous overproduction of aldosterone, with resultant hypertension, suppression of the renin-angiotensin system, and decreased plasma renin activity. Primary hyperaldosteronism is caused by one of three conditions :

Bilateral idiopathic hyperaldosteronism, *characterized by bilateral nodular hyperplasia of aldosterone-secreting zona glomerulosa cells of the adrenal glands, is the most common underlying cause, accounting for about 60% of cases, most of which are sporadic.*

Adrenocortical neoplasm, *either an aldosterone-producing adenoma (the most common cause) or, rarely, an adrenocortical carcinoma. In approximately 35% of cases, primary hyperaldosteronism is caused by a solitary aldosterone-secreting adenoma, a condition referred to as Conn syndrome.*

Familial hyperaldosteronism *accounts for ~5% of cases.*

MORPHOLOGY :Aldosterone-producing adenomas are almost always solitary, small (<2 cm in diameter), well-circumscribed lesions, more often found on the left than on the right. In general, the cells tend to be uniform in size and shape; occasionally, there is modest nuclear and cellular pleomorphism (see Fig. 24.51). A characteristic feature of aldosterone-producing adenomas is the presence of eosinophilic, laminated cytoplasmic inclusions, known as spironolactone bodies, found after treatment with the antihypertensive drug spironolactone.

Adrenogenital Syndromes

Disorders of sexual differentiation, such as virilization or feminization, can be caused by primary gonadal disorders and several primary adrenal disorders. The adrenal cortex secretes dehydroepiandrosterone and androstenedione, two compounds that can be converted to testosterone in peripheral tissues.

Adrenocortical Insufficiency

Adrenocortical insufficiency, or hypofunction, may be caused by primary adrenal disease (primary hypoadrenalism) or decreased stimulation of the adrenals due to a deficiency of ACTH (secondary hypoadrenalism). Three major patterns of adrenocortical insufficiency are recognized: (1) primary acute adrenocortical insufficiency (adrenal crisis), (2) primary chronic adrenocortical insufficiency (Addison disease), and (3) secondary adrenocortical insufficiency.

Primary Acute Adrenocortical Insufficiency *Acute adrenal cortical insufficiency occurs in a variety of clinical settings.*

- *In individuals with chronic adrenocortical insufficiency, a crisis may be precipitated by any form of stress that requires an immediate increase in steroid output to maintain homeostasis*
- *In patients maintained on exogenous corticosteroids, in whom rapid withdrawal of steroids or failure to increase steroid doses in response to an acute stress may precipitate an adrenal crisis because of the inability of the atrophic adrenals to produce glucocorticoid hormones.*

As a result of massive adrenal hemorrhage, which damages the adrenal cortex sufficiently to cause acute adrenocortical insufficiency—as occurs in newborns following prolonged and difficult delivery with considerable trauma and hypoxia. It also occurs in some patients maintained on anticoagulant therapy, in postsurgical patients who develop disseminated intravascular coagulation and consequent hemorrhagic infarction of the adrenals, and as a complication of disseminated bacterial infection; in this last setting, it is called Waterhouse-Friderichsen syndrome.

Primary Chronic Adrenocortical Insufficiency (Addison Disease)

Addison disease, or chronic adrenocortical insufficiency, is an uncommon disorder resulting from progressive destruction of the adrenal cortex. Typically, clinical manifestations of adrenocortical insufficiency do not appear until at least 90% of the adrenal cortex has been compromised

Pathogenesis

A large number of diseases may affect the adrenal cortex, including lymphoma, amyloidosis, sarcoidosis, hemochromatosis, fungal infections, and adrenal hemorrhage, but more than 90% of all cases are attributable to one of four disorders: autoimmune adrenalitis, tuberculosis, AIDS, or metastatic cancers.

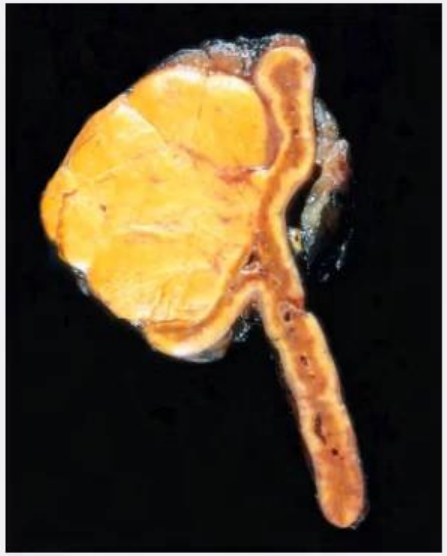
Clinical features

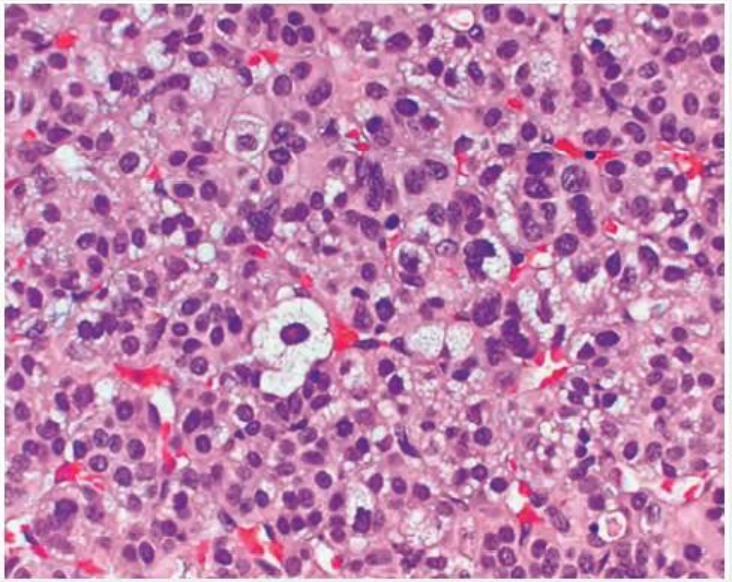
Patients typically present with fatigue, weakness, and gastrointestinal disturbances. Primary adrenocortical insufficiency also is characterized by high ACTH levels with associated skin pigmentation. Secondary Adrenocortical Insufficiency Any disorder of the hypothalamus and pituitary, such as metastatic cancer, infection, infarction, or irradiation, that reduces the output of ACTH leads to a syndrome of hypoadrenalism that has many similarities to Addison disease. Analogously, prolonged administration of exogenous glucocorticoids suppresses the output of ACTH and adrenal function. With secondary disease, the hyperpigmentation of primary Addison disease is lacking, because levels of melanocyte-stimulating hormone are not elevated.

Adrenocortical Neoplasms

adrenocortical adenomas:

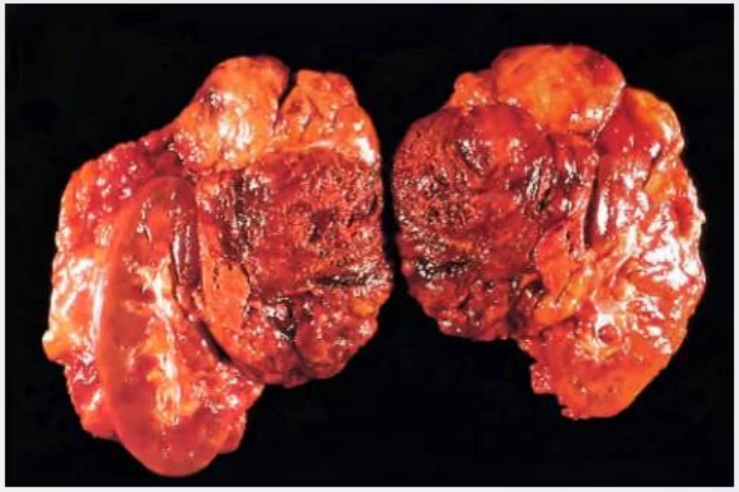
MORPHOLOGY *Most adrenocortical adenomas are clinically silent and are usually incidental findings at autopsy or during abdominal imaging for an unrelated cause. The typical cortical adenoma is a well-circumscribed, nodular lesion up to 2.5 cm in diameter that expands the adrenal. In contrast to a functional adenoma, which is associated with atrophy of the adjacent cortex, the cortex adjacent to a nonfunctional adenoma is normal. On cut surface, adenomas are usually yellow to yellow-brown because of the presence of lipid. Microscopically, adenomas are composed of cells similar to those populating the normal adrenal cortex. The nuclei tend to be small, although some degree of pleomorphism may be encountered, even in benign lesions ("endocrine atypia")*

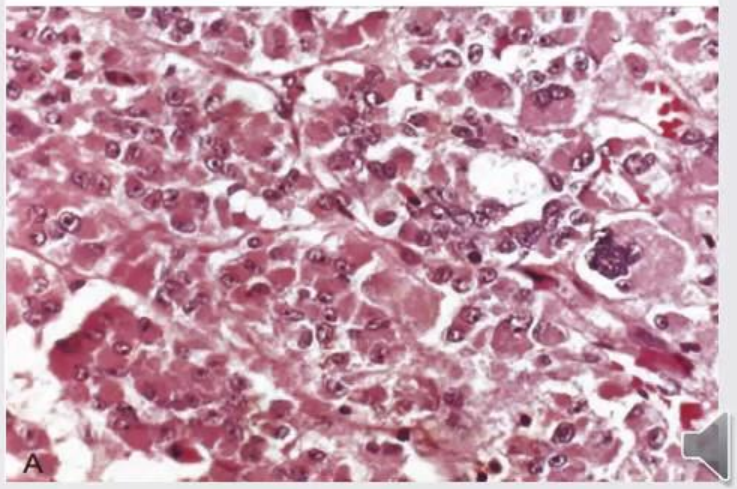




Adrenocortical carcinomas

are rare neoplasms that have a bimodal distribution in the first and fifth decades of life. They are more likely to be functional than adenomas and are often associated with virilism or other clinical manifestations of hyperadrenalism. In most cases, adrenocortical carcinomas are large, invasive lesions, many exceeding 20 cm in diameter, which efface the native adrenal gland





MORPHOLOGY:

On cut surface, adrenocortical carcinomas are typically variegated, poorly demarcated lesions containing areas of necrosis, hemorrhage, and cystic change. Adrenal cancers have a strong tendency to invade the adrenal vein, vena cava, and lymphatics. Metastases to regional and periaortic nodes are common, as is distant hematogenous spread to the lungs and other viscera. The median patient survival is about 2 years. Microscopically, adrenocortical carcinomas may be composed of well-differentiated cells, resembling those seen in cortical adenomas, or bizarre, monstrous giant cells

Adrenal Medulla The adrenal medulla is a large paraganglion similar to paraganglia in the sympathetic chain. Catecholamines produced in the medulla are released directly into the bloodstream. Paraganglioma Pheochromocytomas are identical to paragangliomas arising in the sympathetic chain. Paragangliomas are tumors of neuroendocrine cells that produce catecholamines, and they may produce hormonal syndrome by releasing hormone chronically or episodically . The episodic release of catecholamines results in a symptom complex with flushing and hypertension that is classically associated with pheochromocytomas. Extra-adrenal paragangliomas can also present with a hormonal syndrome or as mass lesions (e.g., carotid body tumor).

MULTIPLE ENDOCRINE NEOPLASIA *Multiple endocrine neoplasia (MEN) comprises two different genetic diseases in which point mutations of the MEN1 gene (in MEN I syndrome) or the RET gene (in MEN II syndrome) result in hyperplasia or tumor formation (or both) in several different endocrine organs. Both MEN I and MEN II syndromes are inherited in an autosomal dominant pattern. MEN I results from alterations in the MEN I tumor suppressor gene that controls SMAD signaling in the TGF-β and other pathways that can inhibit cell proliferation. These patients tend to develop hyperplasia or adenomas of parathyroid glands, islet cell tumors of the pancreas, as well as pituitary adenomas, which usually are not prolactinomas but may occasionally produce growth hormone.*

MEN II is caused by mutations in the RET proto-oncogene, which is altered in the majority of sporadic papillary thyroid cancers (see Papillary Carcinoma section). MEN II patients have activating mutations in RET, and almost all develop medullary carcinomas of the thyroid gland as they age. Some patients have pheochromocytomas as well. MEN II patients are usually managed by prophylactic thyroidectomy because of the near certainty of their developing medullary thyroid carcinoma (a potentially deadly cancer). Two different forms of MEN II are recognized (Table 10-1), and differences may be related to the nature of the RET gene mutations in different kindreds. Some MEN IIA patients develop hyperparathyroidism, but MEN IIB patients do not. MEN IIB patients develop ganglioneuromas in the gastrointestinal tract.

TABLE 10-1. Multiple Endocrine Neoplasia (MEN) syndromes

	Incidence		
Disease	**Type I**	**Type IIA**	**Type IIB**
MEN I (MEN1 gene)			
Parathyroid hyperplasia	Almost all		
Pancreatic endocrine tumor	1/3		
Pituitary adenoma	1/3		
MEN II (RET gene)			
Medullary thyroid carcinoma		All	All
Pheochromocytoma		1/2	1/2
Parathyroid hyperplasia		1/3	None
Ganglioneuroma		None	Most