ADRENAL CANCERS

Kenneth Alonso, MD, FACP

Anatomy and embryology

- The adrenal cortex is derived from mesoderm. The medulla, from neural crest cells.
- The superior adrenal artery branches from the inferior phrenic; the middle adrenal artery, from the superior mesenteric; the inferior adrenal artery, from the renal artery.
- The left adrenal vein empties into the left renal vein; the right adrenal vein empties directly into the inferior vena cava.

Glucocorticoid excess

- Central obesity with striae
- Round and plethoric facies (compare photos from different years)
- Hypertension
- Hirsutism
- Menstrual disturbance
- In children, virilization with or without salt wasting is the common presentation.
- 21 β-hydroxylase deficiency may be a late onset disease and is seen in 5-25% of women with adrenal hormone excess.

Glucocorticoid excess

Table 24-9 Clinical Features of Cushing Syndrome

Feature	Percent
Obesity or weight gain	95%*
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%

*100% in children.
Adapted from Newell-Price J, et al: Cushing syndrome. Lancet 367:1605-1616, 2006.

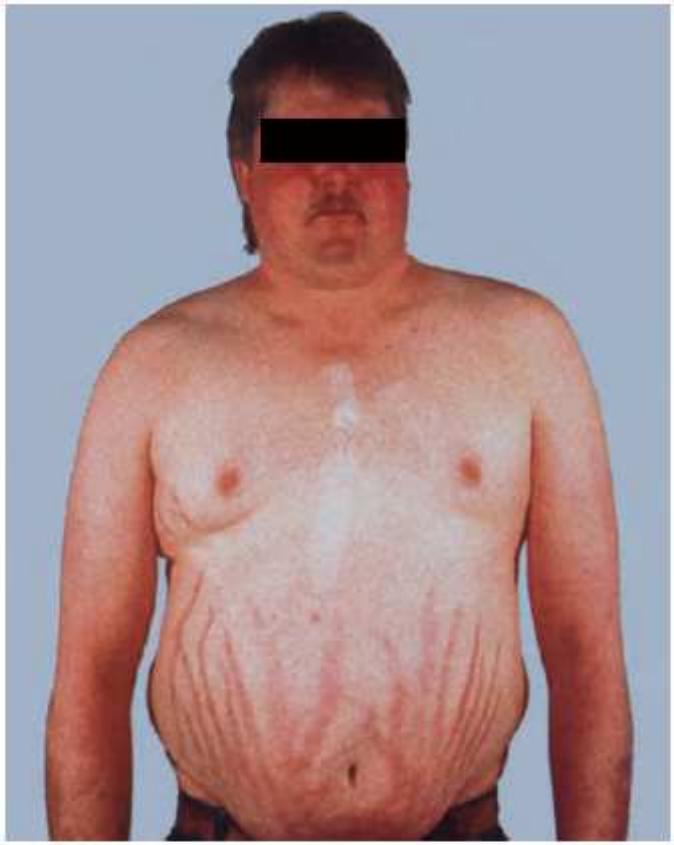


Figure 24-44 A patient with Cushing syndrome demonstrating central obesity, "moon facies," and abdominal striae. (Reproduced with permission from Lloyd RV, et al (eds): Atlas of Nontumor Pathology: Endocrine Diseases. Washington, DC, American Registry of Pathology, 2002.)

Table 24-8 Endogenous Causes of Cushing Syndrome

Cause	Relative Frequency (%)	Ratio of Females to Males
ACTH-Dependent		
Cushing disease (pituitary adenoma; rarely CRH	70	3.5:1
Ectopic corticotropin syndrome (ACTH)	10	1:1
ACTH-Independent		
Adrenal adenoma	10	4:1
Adrenal carcinoma	5	1:1
Macronodular hyperplasia (ectopic expression of hormone receptors, including GIPR, LHR, vasopressin and serotonin receptors)	<2	1:1
Primary pigmented nodular adrenal disease (*PRKARIA* and *PDE11* mutations)	<2	1:1
McCune-Albright syndrome (*GNAS* mutations)	<2	1:1

ACTH, Adrenocorticotropic hormone; GIPR, gastric inhibitory polypeptide receptor; LHR, luteinizing hormone receptor; *PRKAR1A*, protein kinase A regulatory subunit 1α; *PDE11*, phosphodiesterase 11A.

Note: These etiologies are responsible for endogenous Cushing syndrome. The most common overall cause of Cushing syndrome is exogenous glucocorticoid administration (iatrogenic Cushing syndrome).

Adapted with permission from Newell-Price J, et al: Cushing syndrome. Lancet 367:1605-1616, 2006.

Glucocorticoid excess

- Exogenous glucocorticoids in supraphysiologic doses are the most common cause of Cushing's syndrome.
- Benign adrenal adenomas are small
- 20% are functional
- Do not produce androgens or mineralocorticoids
- Fewer than 2% of adrenal masses greater than 4cm in size are adenomas
- In half of pregnant patients, the cause of the excess is an adrenal tumor.

Glucocorticoid excess

- If greater than 6cm, 92% are carcinomas
- Adrenal cortical carcinoma usually has a rapid clinical course
- May present with mass effects
- May present with virilization, and, rarely, feminization (rarely)
- 60% of adrenal carcinomas are hyperfunctional
- IGF-2 overexpressed.
- MDR-1 (p-glycoprotein pump) and ERCC-1 (excision repair) mutated.

Glucocorticoid excess

- Hyperplastic adrenal tissue over-expresses receptors for LH, ADH, gastric inhibitory peptide, and serotonin.
- This regulates ACTH production in a manner not understood.
- GNAS mutations ($G_s\alpha$ activation) in McCune-Albright syndrome affect cAMP levels
- PRKR1A mutations affect cAMP levels
- PDE11A (phosphodiesterase) mutation leads to elevated cAMP levels (failure of enzyme degradation)

Histopathology

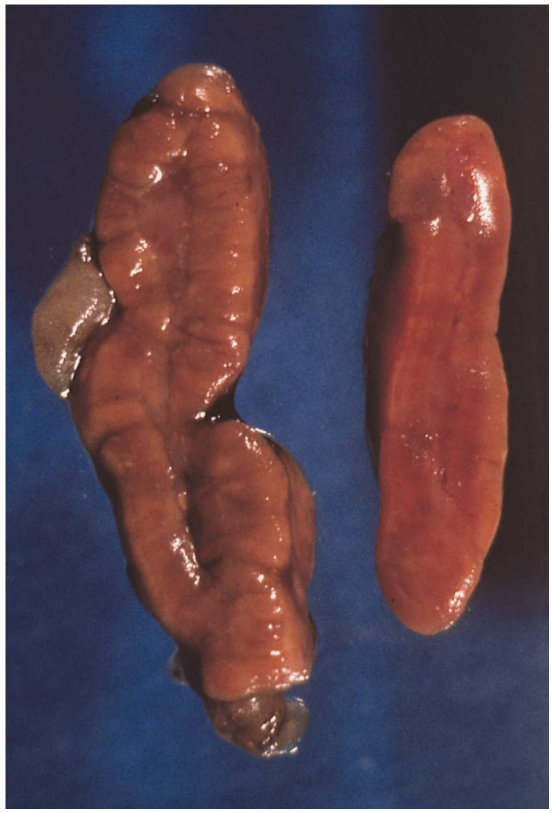
- Adrenal
- Exogenous glucocorticoid excess suppresses endogenous ACTH
- Bilateral cortical atrophy due to a lack of stimulation of the zonae fasciculata and reticularis by ACTH.
- The zona glomerulosa is of normal thickness because this portion of the cortex functions independently of ACTH

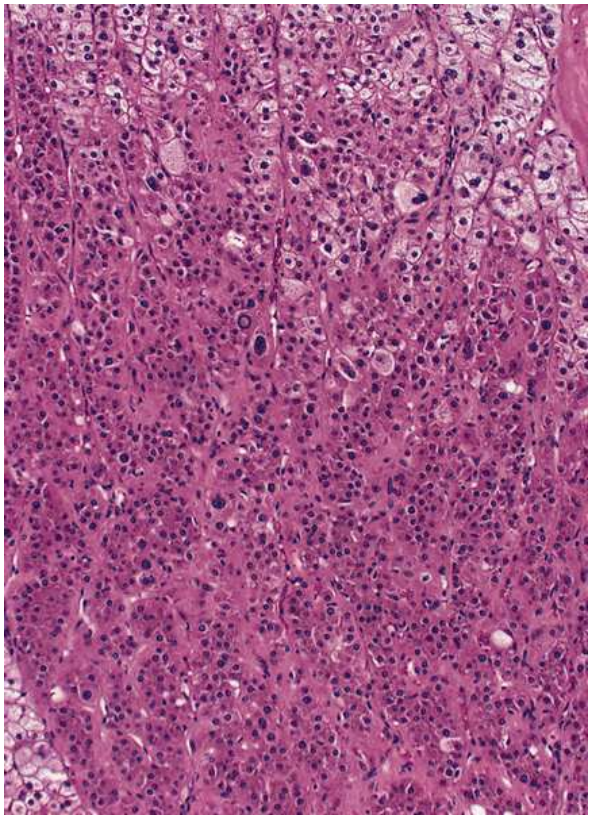
Histopathology

- Diffuse hyperplasia is found in individuals with ACTH-dependent Cushing syndrome.
- Both glands are enlarged and yellow.
- The adrenal cortex is diffusely thickened and variably nodular,
- Microscopically, the hyperplastic cortex demonstrates an expanded “lipid-poor” zona reticularis, comprising compact, eosinophilic cells, surrounded by an outer zone of vacuolated “lipid-rich” cells, resembling those seen in the zona fasciculata.
- Any nodules present are usually composed of vacuolated “lipid-rich” cells.

Figure 24-42 Diffuse hyperplasia of the adrenal contrasted with normal adrenal gland. In cross-section the adrenal cortex is yellow and thickened, and a subtle nodularity is seen (contrast with Fig. 24-46). Both adrenal glands were diffusely hyperplastic in this patient with ACTH-dependent Cushing syndrome.

Cushing’s disease





Transverse sections of a 3.5 g adrenal gland surgically resected from an 8-year-old boy with recurrent Cushing's disease. (Gross). Much of zona fasciculata is converted to cells with compact, eosinophilic cytoplasm under the trophic influence of ACTH. (Microscopic).

Figs. 3-16 and 3-17

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Histopathology

- In macronodular hyperplasia the adrenals are almost entirely replaced by prominent nodules of varying sizes, which contain an admixture of lipid-poor and lipid-rich cells.
- Micronodular change is present in intervening areas
- Micronodular hyperplasia is composed of small, darkly pigmented (brown to black) nodules, with atrophic intervening areas.

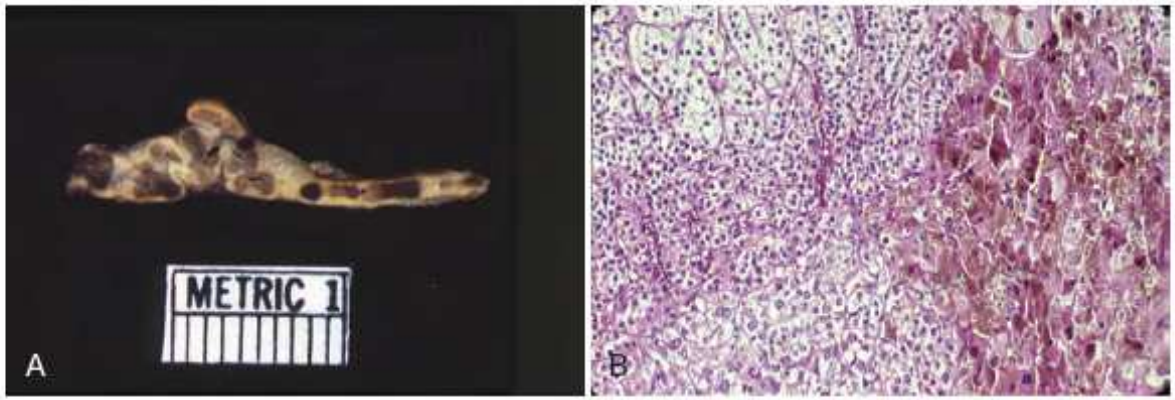
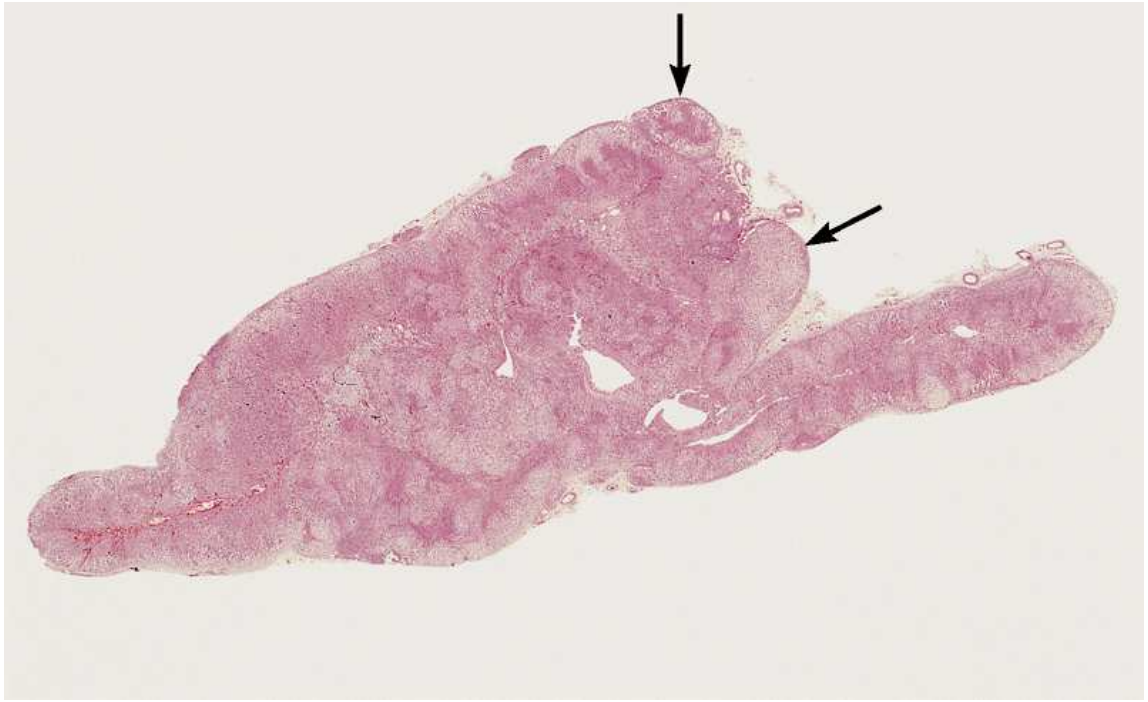


Figure 24-43 **A,** Micronodular adrenocortical hyperplasia with prominent pigmented nodules in the adrenal gland. **B,** On histologic examination the nodules are composed of cells containing lipofuscin pigment, seen in the right part of the field. (Photographs courtesy Dr. Aidan Carney, Department of Medicine, Mayo Clinic, Rochester, Minn.)

Histopathology

- Pituitary
- The most common alteration resulting from high levels of endogenous or exogenous glucocorticoids is Crooke hyaline change.
- The normal granular, basophilic cytoplasm of the ACTH-producing cells in the anterior pituitary becomes homogeneous and paler as a result of the accumulation of intermediate keratin filaments in the cytoplasm

Nodular adrenal gland



Nodular adrenal gland at autopsy of a patient with no evidence of hypercorticolism.
A dominant macronodule can simulate an adrenal cortical adenoma. Other smaller nodules were also present.

Fig. 3-2

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Histopathology

- Adrenocortical adenomas are yellow tumors surrounded by thin or well-developed capsules.
- Microscopically, they are composed of cells that are similar to those encountered in the normal zona fasciculata.
- The carcinomas associated with Cushing syndrome tend to be larger than the adenomas.
- With functioning tumors, both benign and malignant, the adjacent adrenal cortex and that of the contralateral adrenal gland are atrophic

Adrenal adenoma

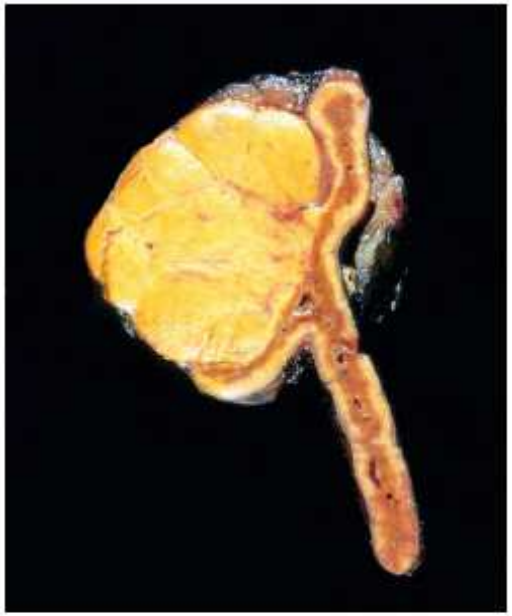


Figure 24-50 Adrenal cortical adenoma. The adenoma is distinguished from nodular hyperplasia by its solitary, circumscribed nature. The functional status of an adrenal cortical adenoma cannot be predicted from its gross or microscopic appearance.

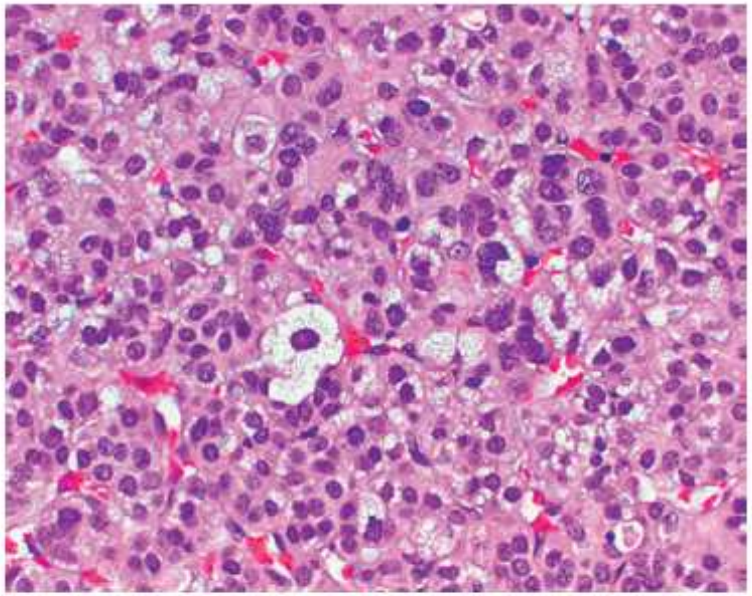
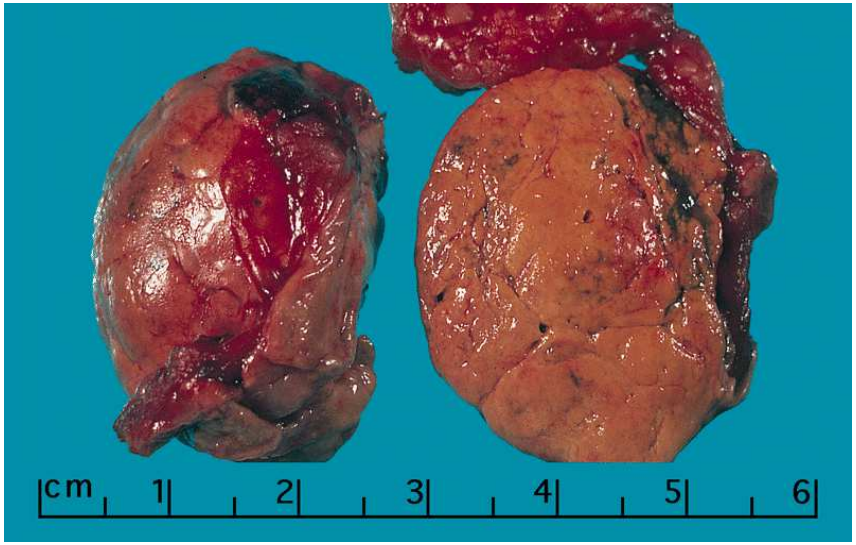
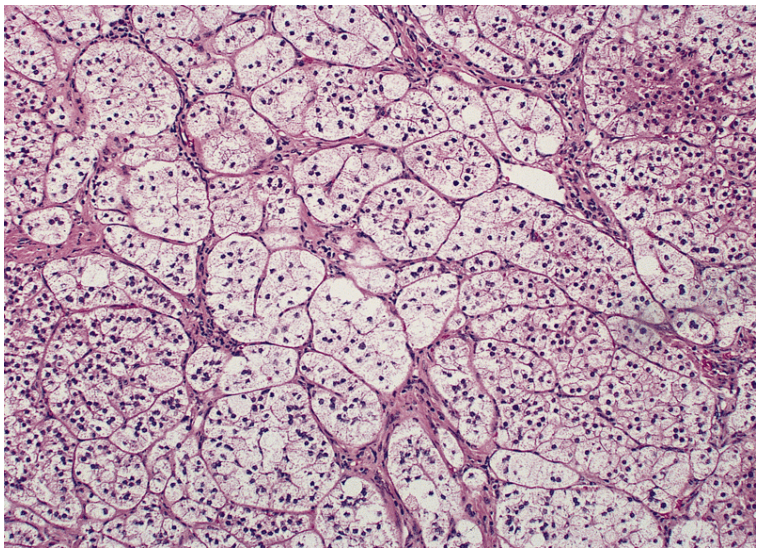


Figure 24-51 Histologic features of an adrenal cortical adenoma. The neoplastic cells are vacuolated because of the presence of intracytoplasmic lipid. There is mild nuclear pleomorphism. Mitotic activity and necrosis are not seen.

Adrenal adenoma



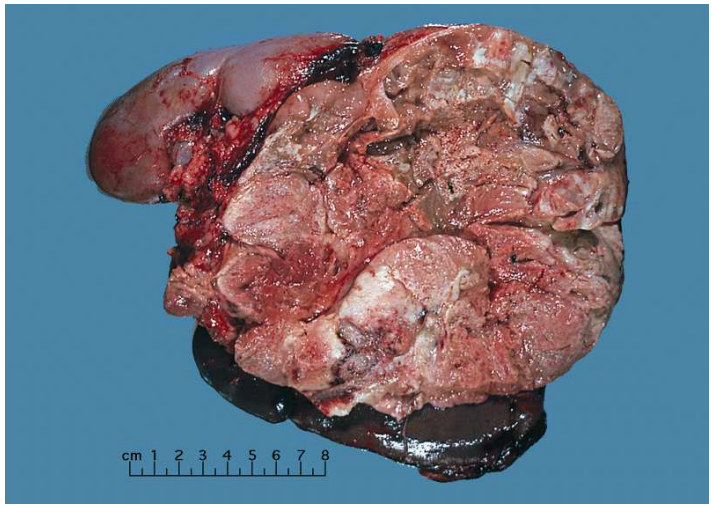


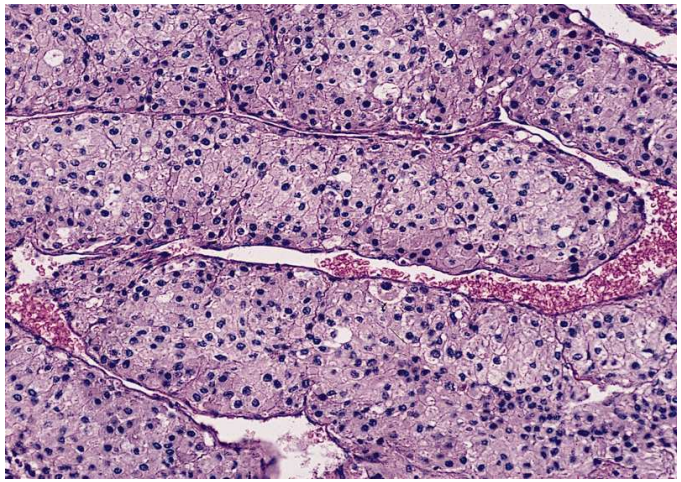
Upper:
The tumor is yellow- orange on cross section and has vague lobulations.
Lower:
The tumor cells are arranged in small clusters and short cords with pale- staining cytoplasm. Note the absence of nuclear enlargement and pleomorphism. Black nodules may contain neuromelanin.

Figs. 4-4 and 4-5

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Adrenal carcinoma





Upper:
The tumor measured invaded kidney and spleen which necessitated en bloc removal of these organs with tumor. Patient had evidence of virilization.
LowerL
Broad anastomosing trabecular pattern with intervening delicate sinusoids. Despite the lack of significant nuclear atypia, this histologic pattern may be associated with aggressive biologic behavior.

Figs. 5-6 and 5-7

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Adrenal carcinoma

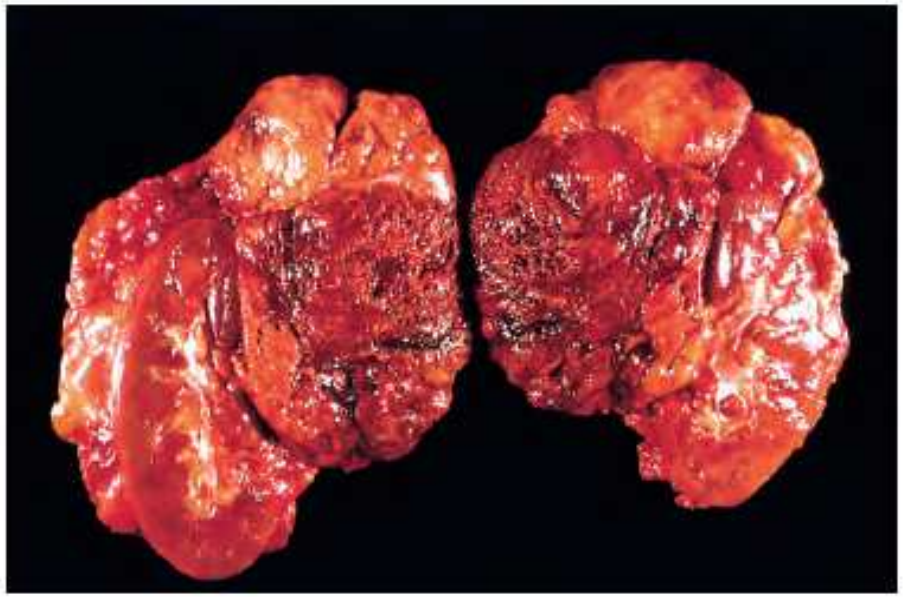


Figure 24-52 Adrenal carcinoma. The hemorrhagic and necrotic tumor dwarfs the kidney and compresses the upper pole.

Adrenal carcinoma

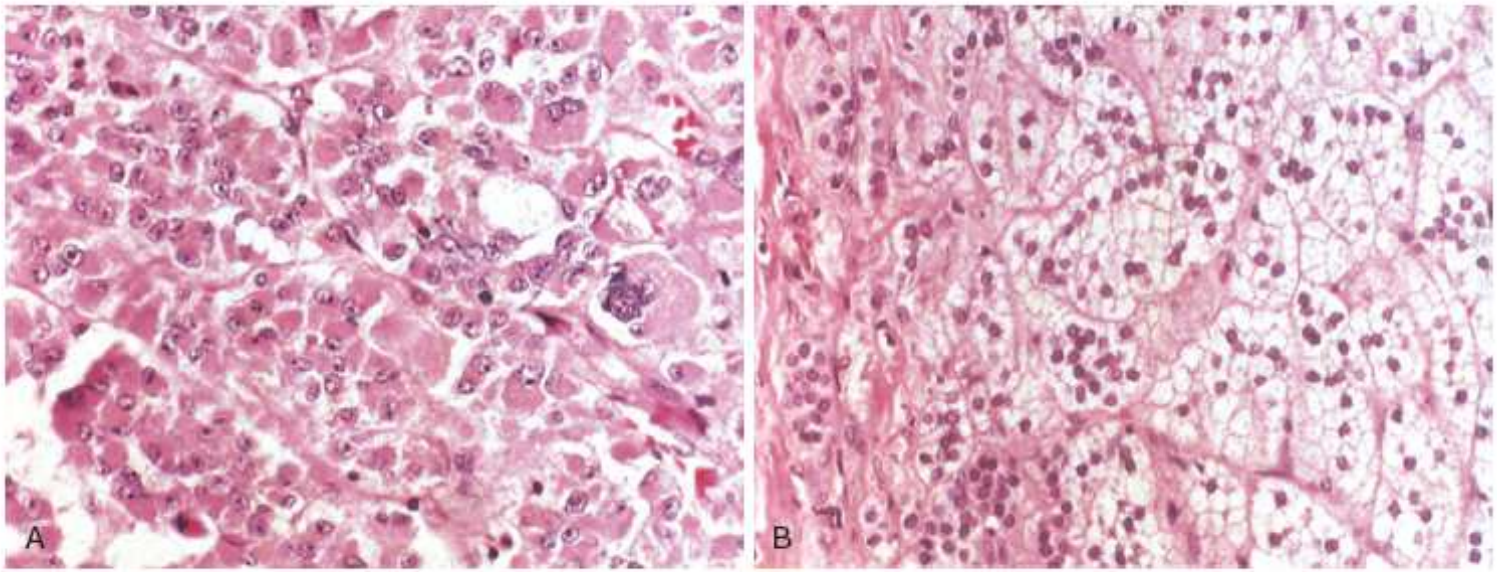


Figure 24-53 Adrenal carcinoma (**A**) revealing marked anaplasia, contrasted with normal adrenal cortical cells (**B**).

Laboratory diagnosis

- 10% of cortisol circulates unbound and is physiologically active.
- Majority is reabsorbed in renal tubules.
- A 24-hour urine free cortisol (UFC) measurement should reflect the integrated cortisol secretion
- Corrected for urine creatinine levels (reflects adequacy of collection).
- Levels may be elevated in depressed patients as well as women with polycystic ovary disease.
- Used for screening for glucocorticoid excess.
- However, a serum cortisol obtained from a sleeping patient at midnight is highly sensitive and specific for glucocorticoid excess.

Laboratory diagnosis

- Administration of 1.0mg dexamethasone followed by determination of an a.m. cortisol level the next day evaluates the hypothalamic-pituitary axis.
- If the morning cortisol is <5ug/dl, the patient does not have adrenal excess.
- Does not suppress adenomas or carcinomas
- Drugs that induce the hepatic enzymatic clearance of dexamethasone reduce plasma dexamethasone concentration (false positive)
- 50% false positive results in women taking oral contraceptives.

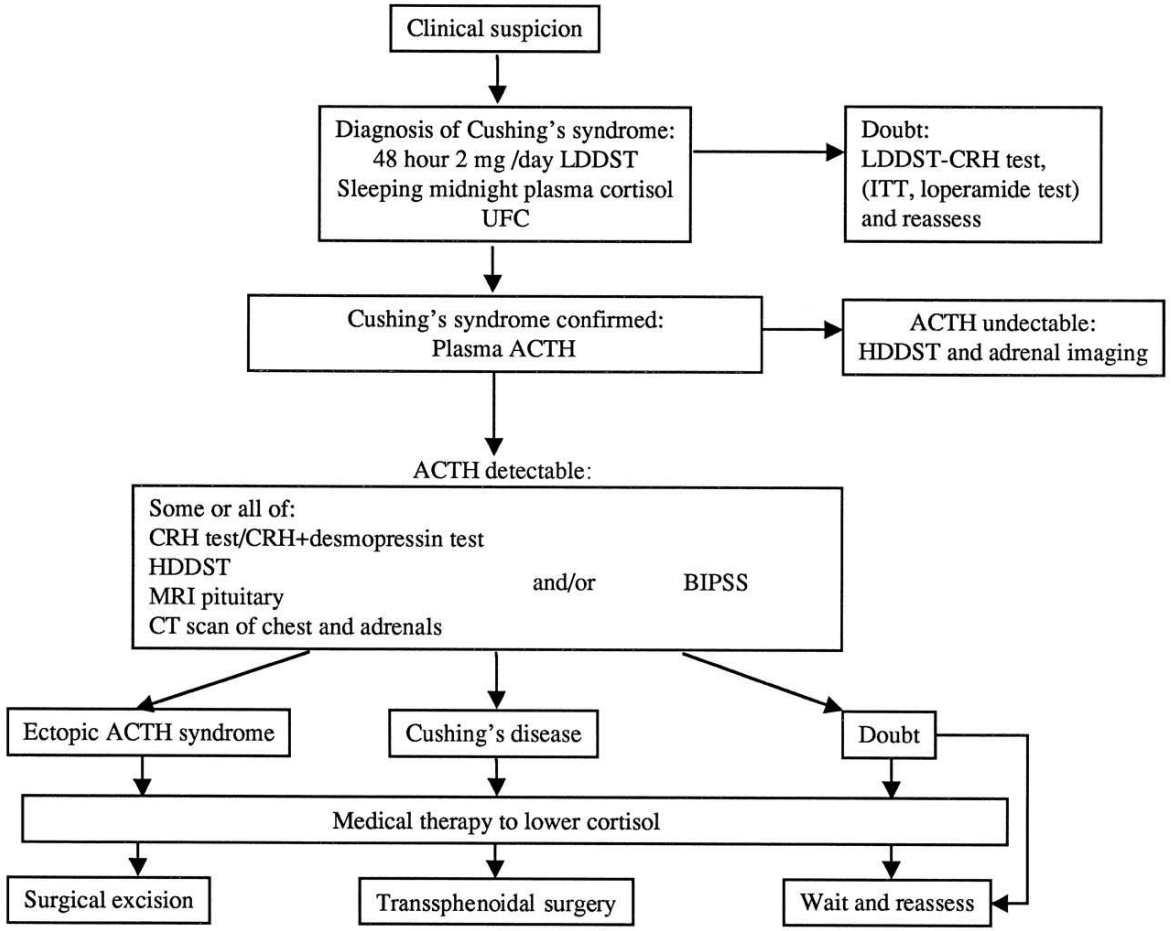
Laboratory diagnosis

- Hyperplastic adrenal tissue possesses hormone receptors and will suppress with 2mg dose dexamethasone.
- Following high dose dexamethasone administration (8mg), ACTH and cortisol levels are measured the following morning.
- ACTH not detectable, cortisol minimally affected: proceed to MRI of adrenal.
- ACTH normal or increased, cortisol not suppressed: proceed to MRI of chest.
- ACTH normal or increased, cortisol may be partially suppressed: proceed to MRI of pituitary.

Endocrine Society strategy

- Screen with one of the following:
- Urine free cortisol
- 1mg dexamethasone overnight suppression (plasma cortisol measured at 8am or urinary free cortisol determined following suppression)
- 2mg dexamethasone suppression over 48 hours (plasma cortisol measured at 8am or urinary free cortisol determined following suppression)
- If the screening test is abnormal, repeat with a second screening test.
- If abnormal, CRH stimulation is performed. If abnormal CRH, proceed to imaging of the pituitary.

Figure 3. A diagnostic approach to the diagnosis and differential diagnosis of Cushing's syndrome.



Endocr Rev, Volume 19, Issue 5, 1 October 1998, Pages 647–672, https://doi.org/10.1210/edrv.19.5.0346

An efficient diagnostic strategy

- No random cortisol determinations
- 24-hour urine free cortisol.
- Cortisol and ACTH drawn at midnight, 8 am, 4 pm during the timed collection.
- If urine free cortisol is elevated, then examine cortisol and ACTH samples.
- If diurnal variation is not lost, consider depression.

An efficient diagnostic strategy

- If cortisol elevated but ACTH low, proceed to MRI of adrenal gland.
- If cortisol elevated and ACTH elevated, proceed to high dose dexamethasone suppression and CRH stimulation.
- If suppresses with dexamethasone and stimulates with CRH, proceed to MRI of pituitary.
- May have to sample inferior petrosal sinus for ACTH
- If no suppression with dexamethasone, look for ectopic source.

Alternative diagnostic strategy

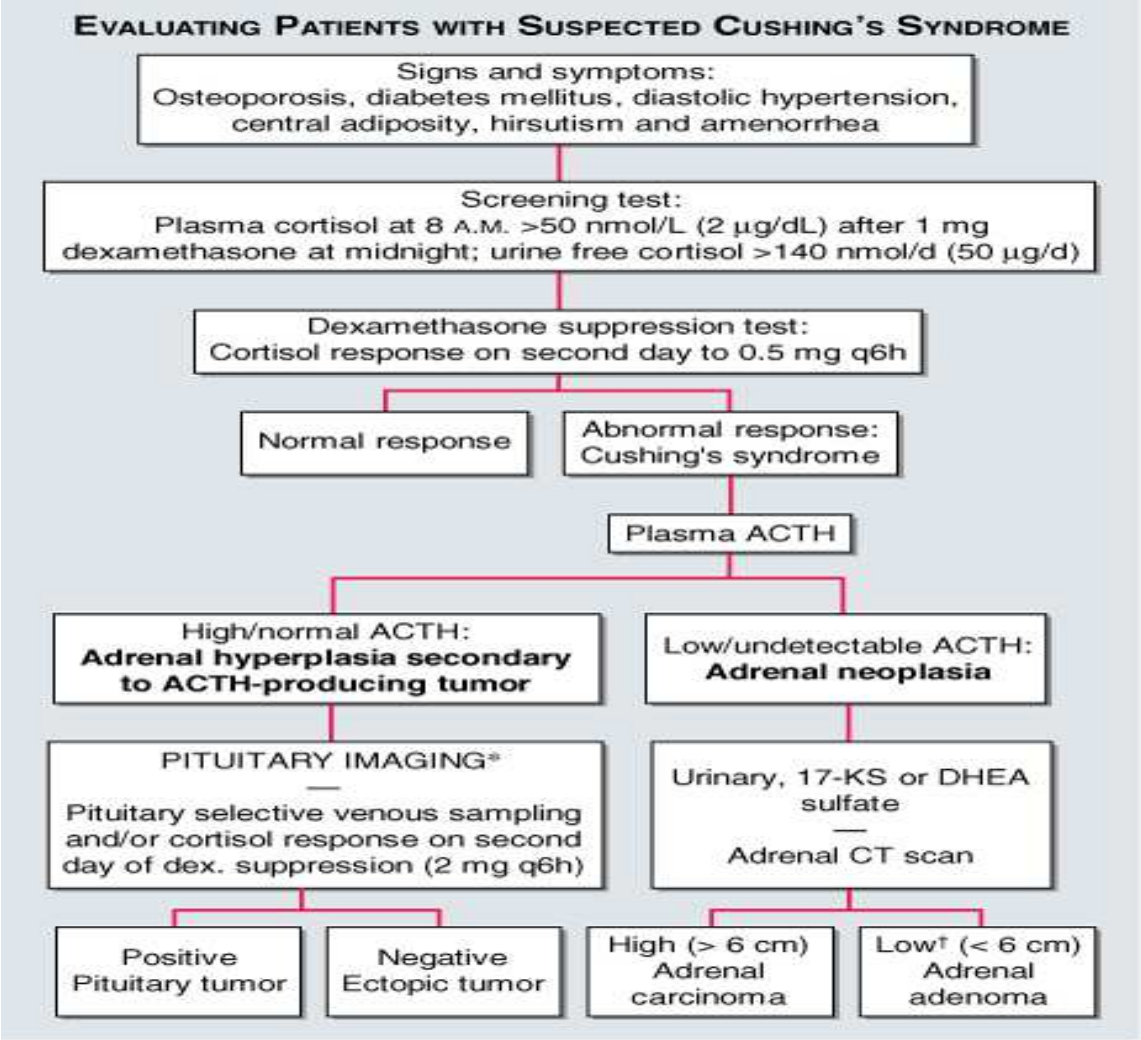


Fig. 336-7
Accessed
02/01/2010

Aldosterone producing tumor

- Present with hypertension, hypokalemia, low renin levels
- Aldosterone levels >15ng/dL, primary hyperaldosteronism
- If 18OH-DOC levels elevated on standing, probably hyperplasia.
- 60% of cases
- If 18OH-DOC levels fall on standing, probably solitary adenoma (Conn's syndrome).
- 35% of cases
- Occasionally bilateral nodular hyperplasia

Aldosterone producing tumor

- 80% of nodules are neoplastic
- <2cm nodules rarely produce visible enlargement
- Generally left-sided
- 67% occur in women, ages 30-40 years

Aldosterone producing tumor

- May see spironolactone bodies in the nodule (eosinophilic)
- Secondary hyperaldosteronism is associated with elevated renin levels
- Mineralocorticoid type I receptors in the kidney are sensitive to both cortisol and aldosterone.
- The kidney has 11-βOH dehydrogenase to locally convert cortisol to cortisone (low affinity).
- Permits aldosterone action.

Adrenal medulla

- Neural crest derivation
- Chromaffin cells (brown-black after exposure to Potassium Dichromate fixative of Zenker) are of sympathetic innervation
- Norepinephrine functions as local neurotransmitter (sympathetic postganglionic neurons) with little hormone circulating
- In contrast, epinephrine enters into circulation
- May produce other bioactive amines

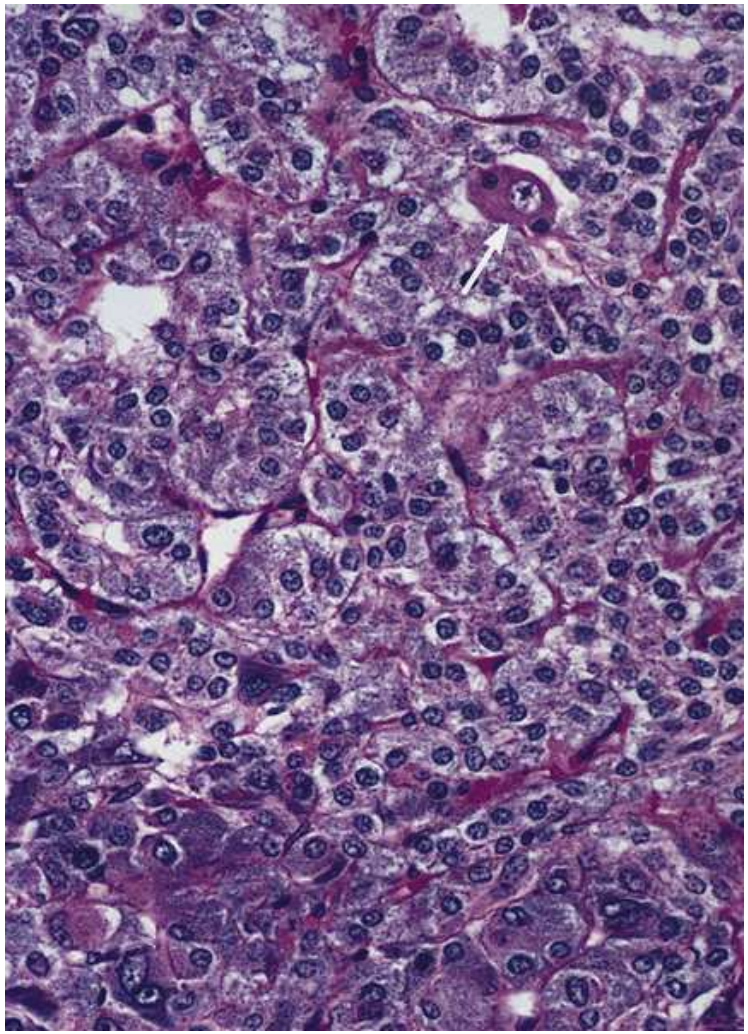
Paraganglion system

- Neuroendocrine cells similar to chromaffin cells
- Together with the adrenal medulla,
- There are three groups based on their anatomic distribution:
- (1) Branchiomeric and (2) Intravagal
- The branchiomeric and intravagal paraganglia associated with the parasympathetic system are located close to the major arteries and cranial nerves of the head and neck and include the carotid bodies
- Intravagal ganglia found along course of vagus nerve

Paraganglion system

- (3) Aorticosympathetic
- Found in association with segmental ganglia of the sympathetic system
- Distributed mainly alongside of the abdominal aorta.
- The organs of Zuckerkandl, close to the aortic bifurcation, belong to this group.
- Bladder

Adrenal medulla



Chromaffin cells contain a myriad of pinpoint cytoplasmic granules. A mature ganglion cell is also apparent (arrow).

Fig. 1-29L

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Pheochromocytoma

- 90% occur below the diaphragm
- 10% extra-adrenal chromaffin negative (paraganglioma)
- 10% associated with MEN syndromes (RET mutation)
- 10% arise in childhood
- 10% not associated with hypertension.
- Of those with hypertension, two-thirds show paroxysmal rise with tachycardia, hyperglycemia, and a sense of apprehension.

Pheochromocytoma

- 10% bilateral
- If VHL mutation, multifocal, peak age in fourth decade
- If NF1 mutation, multifocal, peak age in fifth decade.
- If familial, 70% usually involved with succinic dehydrogenase, or SDHB,SDHC, SDHD mutations
- SDHD AF2 encodes folic acid; SDH mutations, promote stabilization of HIF-1α.

Pheochromocytoma

- SDHC and SDHD associated with head and neck locations;
- SDHB associated with bilateral lesions, extra-adrenal locations, and are frequently malignant. Renal cell carcinoma and gastrointestinal stromal tumors found in 35-70% of those harboring this mutation.
- SDH, VHL mutated tumors are pseudo-hypoxic.
- RET, NF1 mutated tumors have abnormal RAS/RAF/ERK activity.

Pheochromocytoma

- 10% malignant (if extra adrenal, 20-40%)
- Only diagnosed if metastases present
- As many as 25% of individuals with pheochromocytoma and paraganglioma harbor a germline mutation
- Usually appear at a young age

Table 24-11 Familial Syndromes Associated with Pheochromocytoma and Extra-adrenal Paragangliomas

Syndrome	Gene	Associated Lesion	Other Features
Multiple endocrine neoplasia, type 2A (MEN-2A)	*RET*	Pheochromocytoma	Medullary thyroid carcinoma Parathyroid hyperplasia
Multiple endocrine neoplasia, type 2B (MEN-2B)	*RET*	Pheochromocytoma	Medullary thyroid carcinoma Marfanoid habitus Mucocutaneous GNs
Neurofibromatosis, type 1 (NF1)	*NF1*	Pheochromocytoma	Neurofibromatosis Café-au-lait spots Optic nerve glioma
Von Hippel-Lindau (VHL)	*VHL*	Pheochromocytoma, paraganglioma *(uncommon)*	Renal cell carcinoma Hemangioblastoma Pancreatic endocrine neoplasm
Familial paraganglioma 1	*SDHD*	Pheochromocytoma, paraganglioma	
Familial paraganglioma 3	*SDHC*	Paraganglioma	
Familial paraganglioma 4	*SDHB*	Pheochromocytoma, paraganglioma	

GN, Ganglioneuroma; *NF1*, neurofibromin; *SDHB*, succinate dehydrogenase complex, subunit B; *SDHC*, succinate dehydrogenase complex, subunit C; *SDHD*, succinate dehydrogenase complex, subunit D.

Adapted with permission from Elder EE, et al: Pheochromocytoma and functional paraganglioma syndrome: no longer the 10% tumor. J Surg Oncol 89:193-201, 2005.

Multiple endocrine neoplasia

- MEN 1
- Werner Syndrome
- 80-95% of patients present with primary hyperparathyroidism by age 40
- Multiple gastrinomas, VIPomas, and insulinomas in pancreas
- Duodenal gastrinoma principal site of gastrin tumor
- Prolactinoma
- Cushing's syndrome
- MEN1 mutation. Menin complexes with and blocks transcriptional activation of JunD
- Loss of p16 and p27 cell cycle regulators

Multiple endocrine neoplasia

- MEN 2A (Sipple Syndrome)
- 95% of cases
- Germline gain of function mutation of RET gene at 10q11.2
- 95% occur in cysteine-rich domain of exon 10
- Codon 634 point mutation most common
- Binds to glial derived neurotropic factor (GDNF)
- Promotes receptor dimerization (recapitulates ligand binding)
- Medullary Thyroid Carcinoma, 100%
- Pheochromocytoma, 40-50%
- Parathyroid Hyperplasia, 10-20%

Multiple endocrine neoplasia

- MEN 2A variant
- Familial Medullary Thyroid Carcinoma
- Present at older age and have more indolent course
- Germline gain of function mutation of RET gene at 10q11.2
- 85% occur in cysteine-rich domain of exon 10
- Codon 634 point mutation most common
- Binds to glial derived neurotropic factor (GDNF)
- Promotes receptor dimerization (recapitulates ligand binding)

Multiple endocrine neoplasia

- MEN 2B Medullary Thyroid Carcinoma
- Point mutation of RET gene at codon 918 of TK 2
- Domain activates receptor TK function and also causes it to phosporoylate C-SRC and C-ABL

- Pheochromocytoma
- Mucosal ganglioneuromas
- Marfanoid habitus
- More aggressive than are 2A tumors
- Present earlier in life than does 2A

Neuroblastoma

- 7-10% all pediatric neoplasms
- 50% diagnosed in infancy
- 40% arise in adrenal medulla
- 25%, Para vertebral region of abdomen
- 15%, posterior mediastinum
- Disialoganglioside (GD2) expressed.
- ALK germline mutation (at 2p23.2-23.1) associated with familial predisposition.
- Affects tyrosine kinase receptors

Histopathology

- In situ neuroblastomas are reported to occur 40 times more frequently than clinically overt tumors.
- The great majority of these silent lesions spontaneously regress, leaving only a focus of fibrosis or calcification in the adult.
- Neuroblastoma is often sharply demarcated by a fibrous pseudo-capsule, but others are far more infiltrative and invade surrounding structures, including the kidneys, renal vein, and vena cava, and envelop the aorta.
- When cut, they are gray-tan. Focal calcification may be noted. Larger tumors may have areas of necrosis and hemorrhage.

Histopathology

- Composed of small, primitive-appearing cells with dark nuclei, scant cytoplasm, and poorly defined cell borders growing in solid sheets.
- Mitotic activity, nuclear breakdown (“karyorrhexis”), and pleomorphism may be prominent.
- The background often demonstrates a faintly eosinophilic fibrillary material (neuropil) that corresponds to neuritic processes of the primitive neuroblasts.
- Homer-Wright rosettes can be found in which the tumor cells are concentrically arranged about a central space filled with neuropil.

Histopathology

- Larger cells having more abundant cytoplasm, large vesicular nuclei, and a prominent nucleolus, representing ganglion cell*s* in various stages of maturation, may be found in tumors admixed with primitive neuroblasts (ganglioneuroblastoma).
- More mature lesions are ganglioneuromas.
- Maturation of neuroblasts into ganglion cells is usually accompanied by the appearance of Schwann cells.

Histopathology

- The presence of a so-called schwannian stroma composed of organized fascicles of neuritic processes, mature Schwann cells, and fibroblasts is a histologic prerequisite for the designation of ganglioneuroblastoma and ganglioneuroma
- Ganglion cells in and of themselves do not fulfill the criteria for maturation.

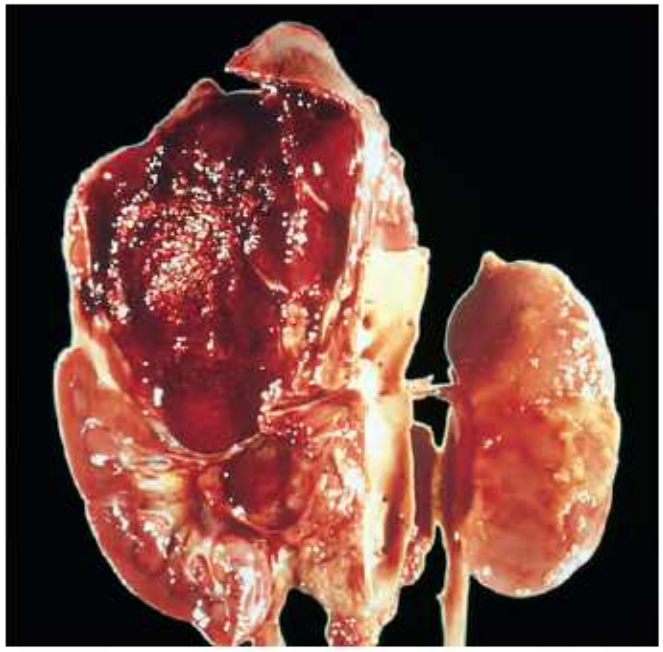


Figure 10-24 Adrenal neuroblastoma in a 6-month-old child. The hemorrhagic, partially encapsulated tumor has displaced the opened left kidney and is impinging on the aorta and left renal artery. (Courtesy Dr. Arthur Weinberg, University of Texas Southwestern Medical School, Dallas, Texas.)

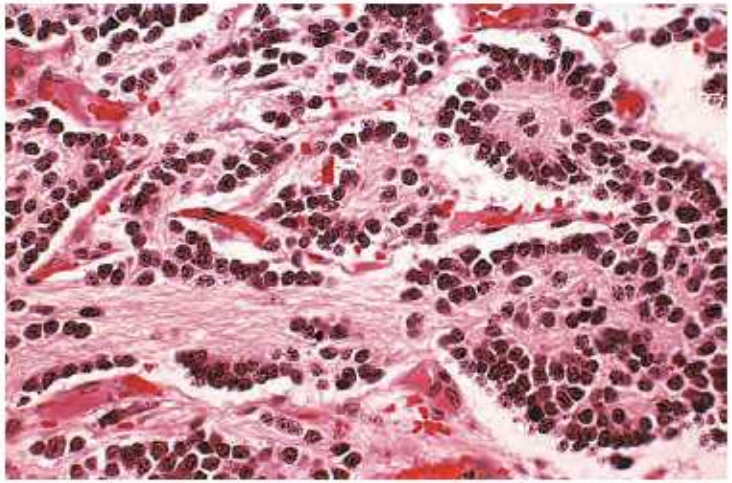


Figure 10-25 Adrenal neuroblastoma. This tumor is composed of small cells embedded in a finely fibrillar matrix.

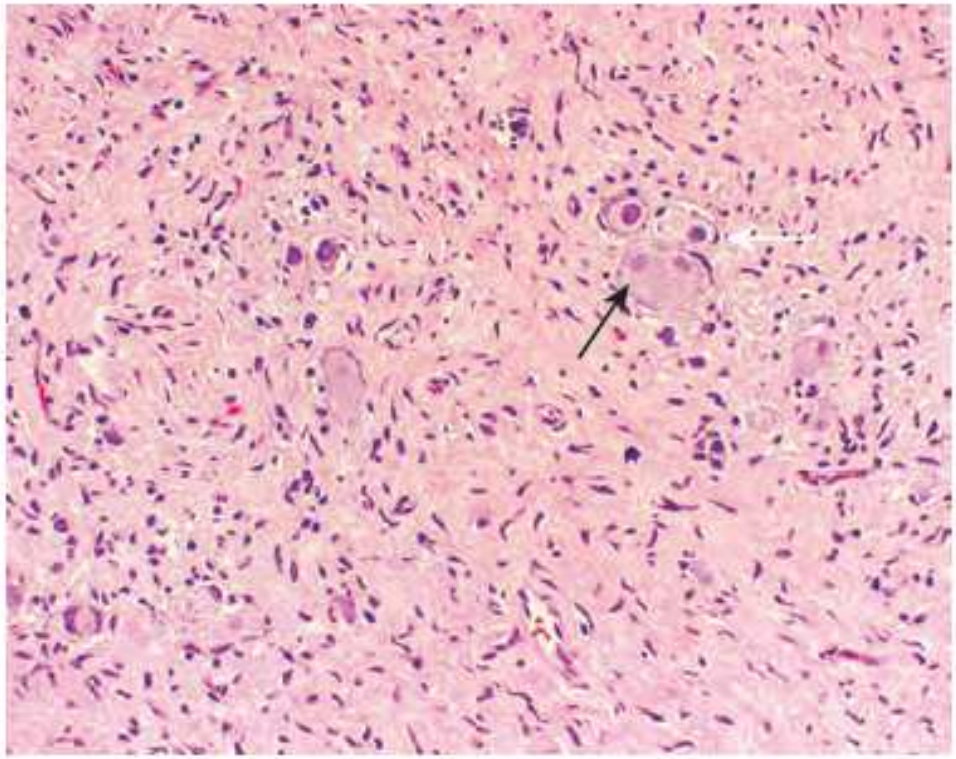


Figure 10-26 Ganglioneuromas, arising from spontaneous or therapy-induced maturation of neuroblastomas, are characterized by clusters of large cells with vesicular nuclei and abundant eosinophilic cytoplasm, representing neoplastic ganglion cells *(arrow)*. Spindle-shaped Schwann cells are present in the background stroma.

Staging

- Stage I is confined to the area of origin (usually, adrenal) with uninvolved nodes.
- Stage II is unilateral with positive ipsilateral node.
- Stage III involves tumor infiltrating across midline OR unilateral tumor with contralateral node involvement OR midline tumor with bilateral node involvement.
- Stage IV is disseminated
- IVS dissemination is limited to liver, skin, or marrow.

Table 10-8 Prognostic Factors in Neuroblastomas

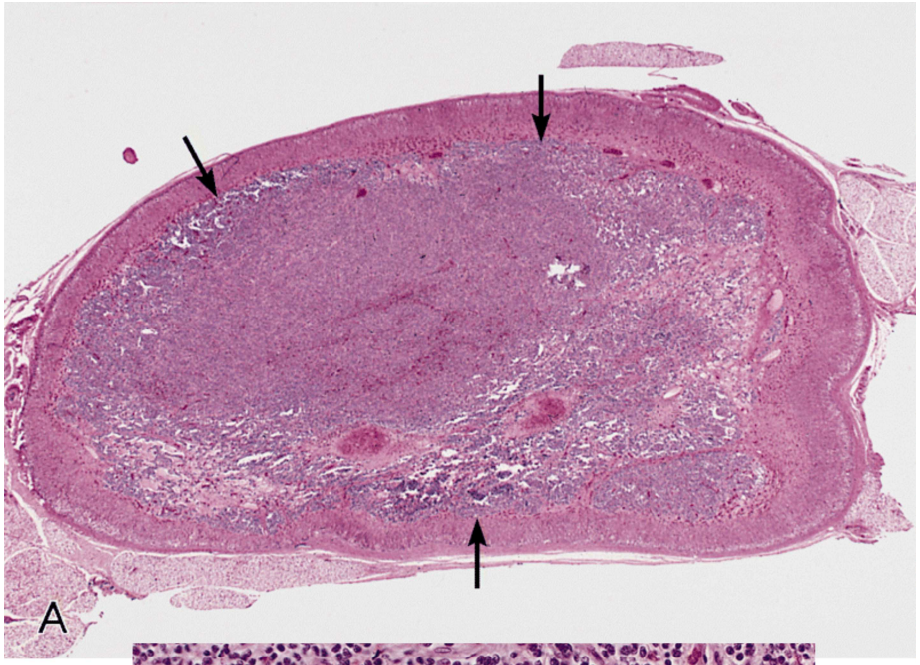
Variable	Favorable	Unfavorable
Stage*	Stage 1, 2A, 2B, 4S	Stage 3, 4
Age*	<18 months	>18 months
Histology*		
Evidence of schwannian stroma and gangliocytic differentiation†	Present	Absent
Mitosis-karyorrhexis index‡	<200/5000 cells	>200/5000 cells
DNA ploidy*	Hyperdiploid (whole chromosomal gains)	Near-diploid (Segmental chromosomal losses; chromothripsis)
*MYCN**	Not amplified	Amplified
Chromosome 1p loss	Absent	Present
Chromosome 11q loss	Absent	Present
TRKA expression	Present	Absent
TRKB expression	Absent	Present
Mutations of neuritogenesis genes	Absent	Present

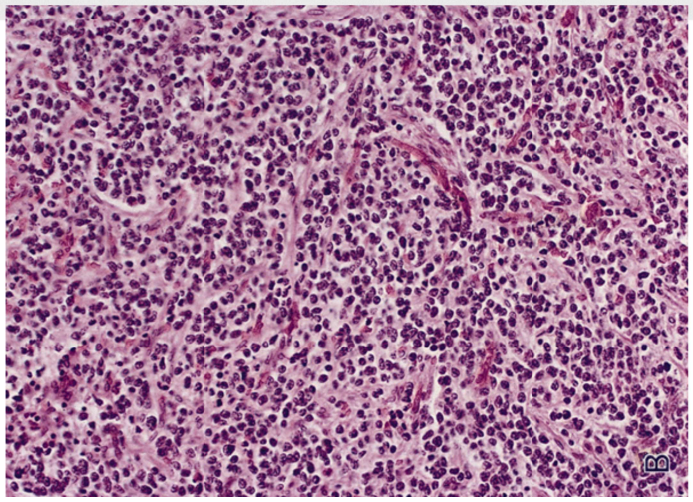
*Corresponds to the most commonly used parameters in clinical practice for assessment of prognosis and risk stratification.
†It is not only the presence but also the amount of schwannian stroma that confers the designation of a favorable histology. At least *50% or more schwannian stroma* is required before a neoplasm can be classified as ganglioneuroblastoma or ganglioneuroma.
‡Mitotic karyorrhexis index (MKI) is defined as the number of mitotic or karyorrhectic cells per 5000 tumor cells in random foci.

Prognostic factors

- Low LDH and age younger than 18 months if no MYC amplification are favorable prognostic factors as is tumor differentiation and presence of tyrosine kinase receptor B.
- Tyrokine kinase receptor A presence is associated with poor prognosis.
- PTRP gene mutation at 9p24.1-p23 unfavorable
- Loss of neurite maturation
- 90% produce catecholamines.
- Vanillmandelic and homovanillic acid elevated in urine.
- Hypertension is not common, however.

Neuroblastoma



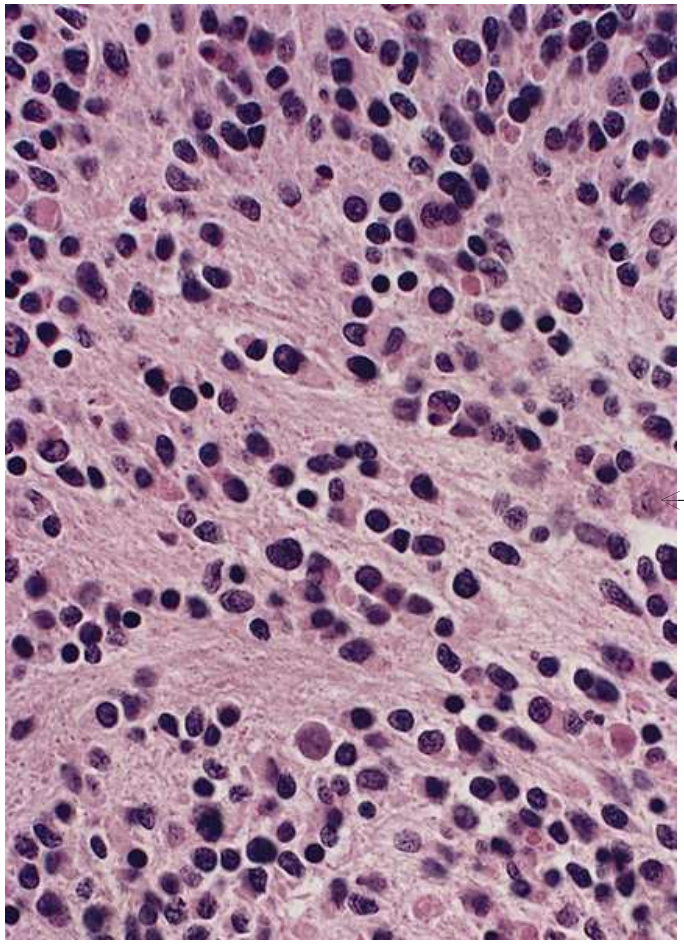


Incidental in situ neuroblastoma
Upper:
The junction with residual adult or definitive cortex is indicated by arrows.
Lower:
Primitive cells are identified.

Figs. 23-7A and 23-7B

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Ganglioneuroblastoma

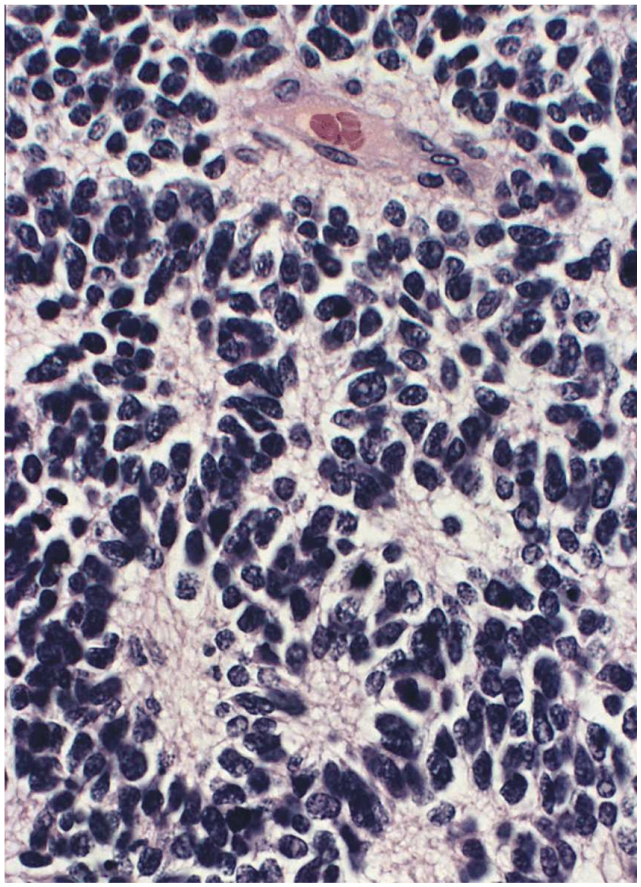


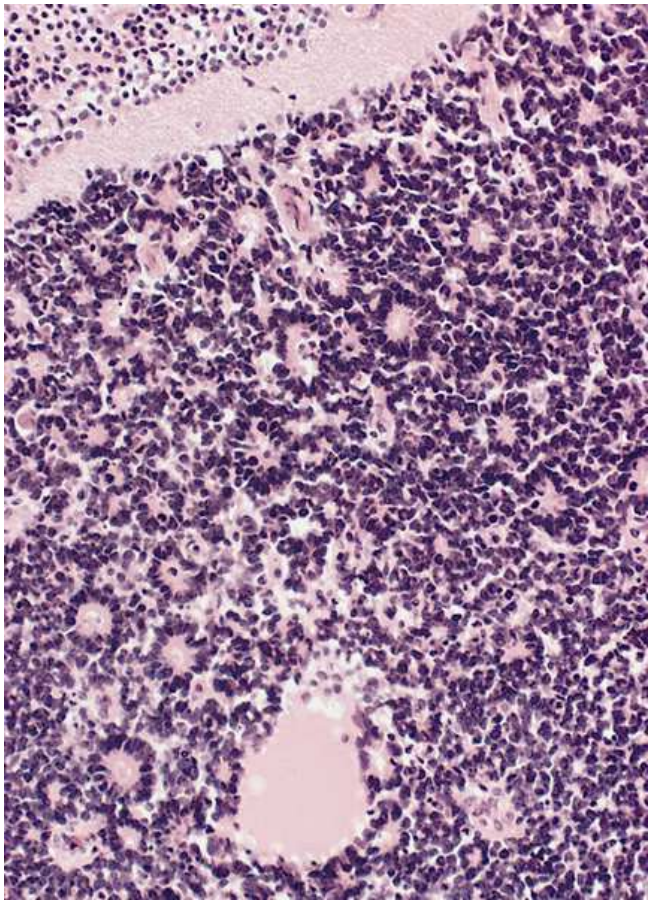
Tumor cells of neuroblastoma are separated by pale pink fibrillar material representing neuritic cell processes. The tumor was largely undifferentiated, with some cells showing early ganglion cell differentiation (arrow added).

Fig. 23-19L

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Rosettes



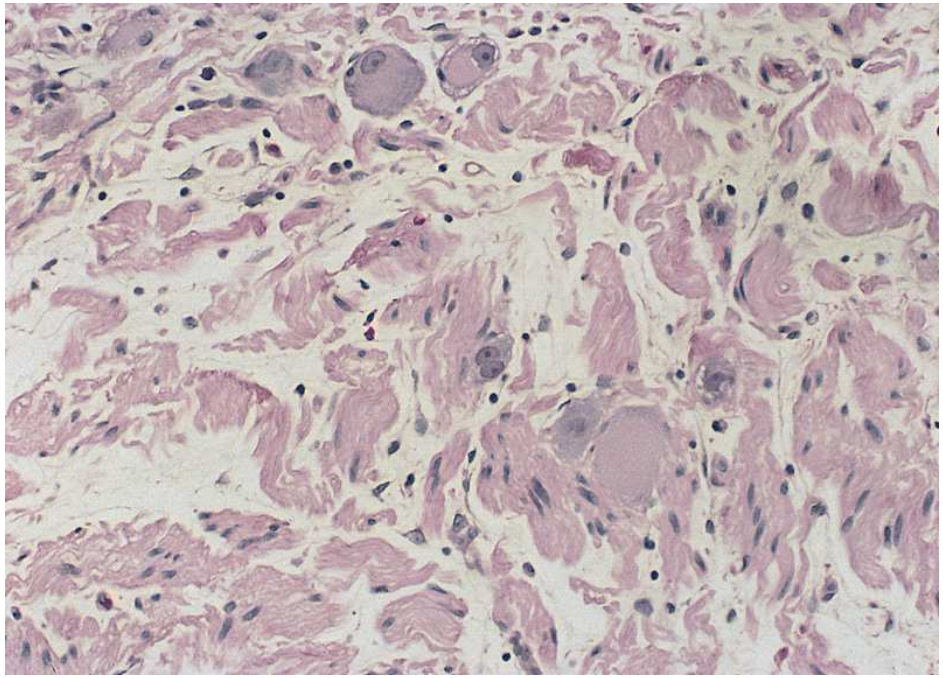


Homer-Wright rosettes in neuroblastoma (Left). Flexner-Wintersteiner rosettes in retinoblastoma. (Right)

Figs. 23-22 and 23-23L

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Ganglioneuroma



This ganglioneuroma is composed of abundant Schwann cells with admixed mature ganglion cells. Some mature ganglion cells were associated with cells resembling satellite cells.

Fig. 23-63

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

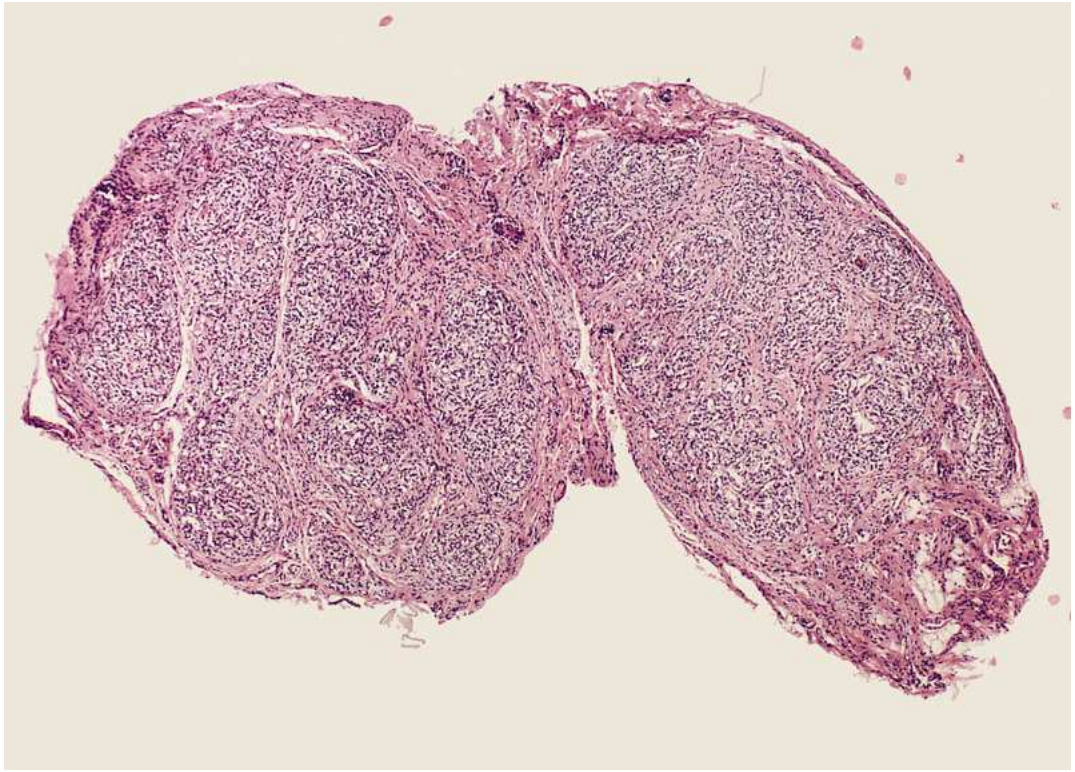
Pathologic criteria for neuroblastoma

- Neuron specific enolase positive
- Catecholamine granules on electron microscopy.
- Mature elements associated with better outcomes.

Pathologic criteria for peripheral neuroectodermal tumor (PNET)

- Brown tumor appearance.
- Polygonal chief cells enveloped in fibrous tissue and sustenacular elongated cells.
- Clear or granular cytoplasm.
- Neurosecretory granules on electron microscopy.
- Neuron specific enolase positive.

Carotid body tumor



Both carotid bodies are from a 38-year-old patient. Note the ovoid shape with multiple lobules. These carotid bodies are well-circumscribed but not truly encapsulated. (X25, Hematoxylin and eosin stain).

Fig. 15-4

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.