Adrenal and Paraganglia Tumors

Adrenal Cortical Tumors

IHC: (+) SF1, Inhibin, Melan-A, Calretinin, Synaptophysin, (-) Chromogranin, Cytokeratin, S100. *Often variable!!*

Adrenal Cortical Adenoma

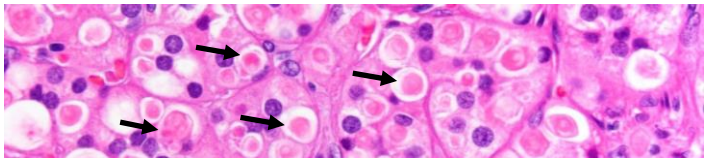
Benign. Very **common**. Often **incidentally** identified. Usually **unilateral solitary** masses with atrophic background adrenal gland.

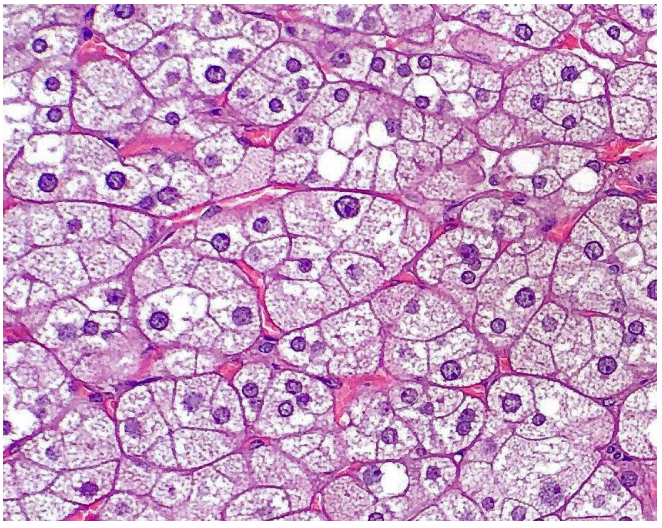
Tumor cells can be lipid-rich (clearer) or lipid-poor (pinker) **arranged in nests and cords** separated by abundant vasculature. Occasional lipofuscin pigment. **Nuclei generally small and round** (occasional extreme "endocrine atypia" is common).
Low/no mitotic activity.
Intact reticulin framework.

On a spectrum with and may hard to differentiate from *hyperplastic nodules*, which is more often multinodular (background hyperplasia) and bilateral.

Associated with MEN1, FAP, Carney Complex, among others…

If aldosterone-secreting adenoma is treated with spironolactone→ "spironolactone bodies" (below)





Can be non-functional (85%) or functional (15%).
Aldosterone-producing→ "*Conn syndrome*"→ hypertension and hypokalemia

Cortisol-producing→ (ACTH-independent) "*Cushing Syndrome*" → central obesity, moon face, hirsutism, poor healing, striae

Sex-hormone-producing→ Rare (more common in carcinomas). Symptoms depend on hormone/sex (virilization or feminization)

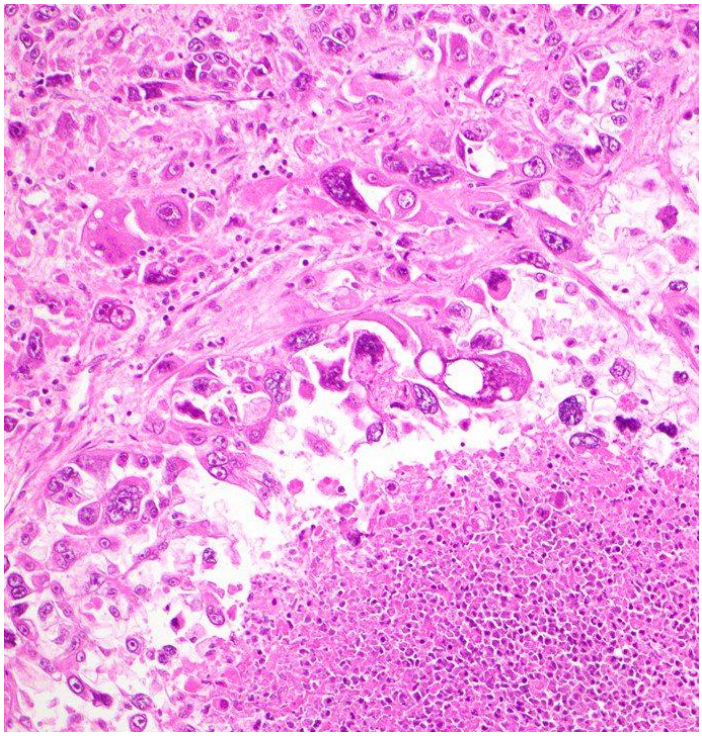
Adrenal Cortical Carcinoma

Malignant.
Most common in older adults.
Can present with an incidental unilateral mass or with an endocrinopathy (see above).

Solid, broad trabeculae, or large nested growth (more diffuse, and larger groups than in adenomas)
Thick **fibrous capsule** with occasional fibrous bands.
Frequent **tumor necrosis.**
Frequent **vascular or capsular invasion**.
Increased **mitotic activity**.

Variants: Oncocytic, Myxoid, Sarcomatoid

Mostly sporadic, but can be associated with Lynch Syndrome and Li-Fraumeni Syndrome



Distinguishing between an Adrenal Cortical Adenoma vs Carcinoma

Weiss Criteria:

Most widely used system, but doesn't work as well in borderline cases or variants.
The presence of **≥3 of these of these criteria correlates with malignant behavior**.

Cannot be used on oncocytic adrenal cortical neoplasms or pediatric adrenal tumors (refer to separate specific grading schemes)

Features *only* seen in metastasizing tumors: ≥6 mitoses per 50 HPF, atypical mitoses, invasion of venous structures.

[PMID: 6703192]

Weiss Criteria (≥3 = Malignant)
High nuclear grade (based of Fuhrman criteria)
Mitotic rate of >5 mitoses per 50 HPF
Atypical mitotic figures
<25% Clear cells
Diffuse architecture
Tumor necrosis
Venous invasion
Sinusoidal invasion
Capsular invasion

"Modified" Weiss Criteria:

Designed to be more reproducible.
Total score of 3 or greater correlates with subsequent malignant behavior

[PMID: 12459628]

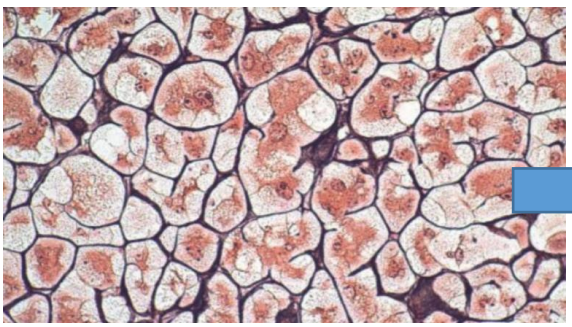
"Modified" Weiss Criteria	Points
Mitotic rate (≥6 mitotic figures/50 HPF)	2
Cytoplasm characteristics, clear vs. compact (compact >75% of cells)	2
Abnormal mitoses	1
Tumor necrosis	1
✚ Invasion of capsule	1

≥3 = Malignant

Reticulin Algorithm:

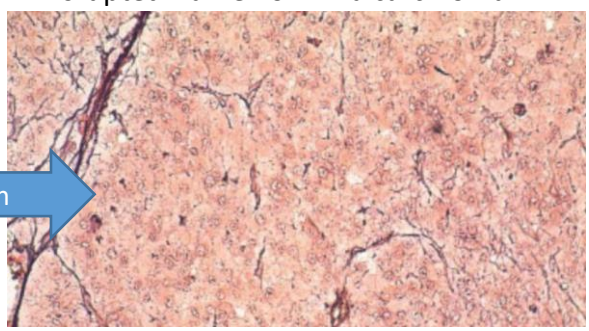
1) Look to see if reticulin framework is intact. If intact throughout→ adenoma, if disrupted, move to step 2.
2) Malignancy is defined by at least one of the following: tumor necrosis, high mitotic rate (>5/50HPF), and venous invasion. [PMID: 23774167]

Intact framework in an adenoma



Loss of Reticulin

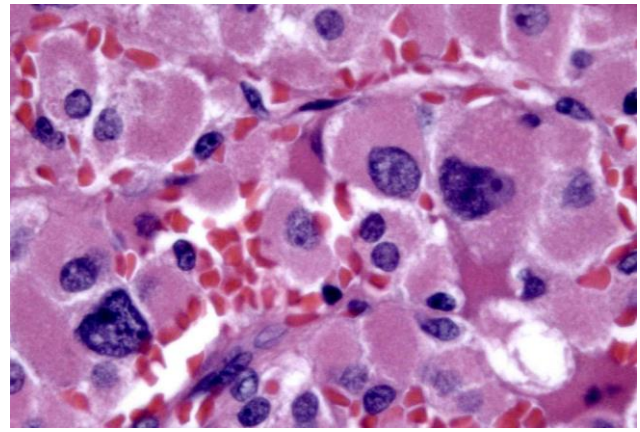
Disrupted framework in a carcinoma



Although this distinction is often straightforward, some borderline cases are likely best categorized as having **"Uncertain Malignant Potential"**.

Although it doesn't fit into the above systems, Ki-67 can also be helpful with this distinction. The proliferation index in adenomas generally <5%, whereas carcinomas have a proliferation index >5%

Oncocytic Adrenocortical Neoplasms



Cells with **abundant granular eosinophilic cytoplasm**.
Many require **>90% of tumor to be oncocytic**.
Mostly non-functional.

Often show areas of nuclear pleomorphism, intranuclear pseudoinclusions, and prominent nucleoli.

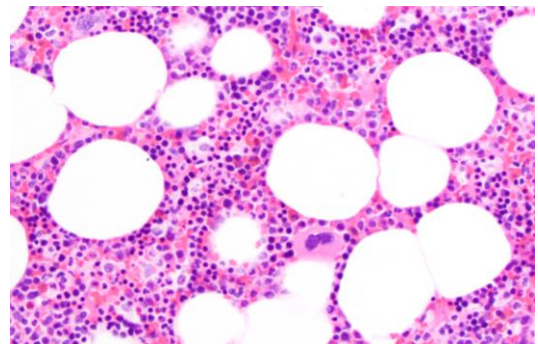
Cannot use Weiss Criteria (use LWB system below).

Lin-Weiss-Bisceglia Criteria:	
Major Criteria	Mitotic rate >5 per 50 HPF
	Atypical mitotic figures
	Venous invasion
Minor Criteria	Size >10 cm and/or weight >200 g
	Tumor necrosis
	Sinusoidal invasion
	Capsular invasion

Lin-Weiss-Bisceglia Criteria:

Used for *Oncocytic* Adrenal Neoplasms
1 major criteria → Malignant→ carcinoma
1-4 minor criteria →Uncertain Malignant Potential
No minor or major → Benign → adenoma
[PMID: 15306935]

Myelolipoma

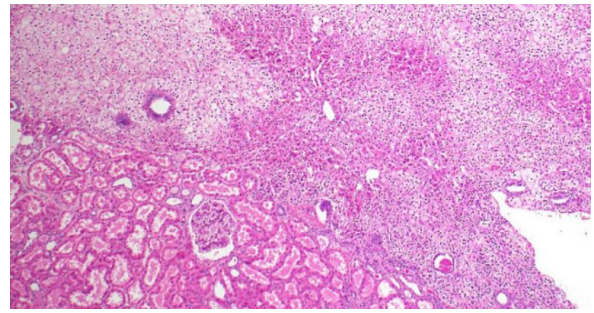


Benign. Composed of **mature fat and bone marrow elements**.
Second most common adrenal neoplasm.
Often older adults presenting with incidental asymptomatic mass.

Can often Dx on imaging due to fat content.

Rare outside of adrenal, can see in pre-sacral region.

Ectopic Adrenal Tissue



Frequent ectopic rests, sometimes fused/embedded with other organs→ Don't mistake for invasion/metastases!!

Common locations: Kidney (adrenal-renal fusion/adhesion), spermatic cord, fallopian tube, liver (hepatoadrenal fusion).

Schwannoma: Benign nerve sheath tumor. Spindled cells with cellular (Antoni A) and hypocellular (Antoni B) areas. Frequent findings: Verocay bodies, lymphoid aggregates, hyalinized vessels. IHC: (+) S100 and SOX10)

Adenomatoid Tumor: Benign mesothelial tumor, as frequently seen associated with GYN/GU tracts. Variably sized tubules in fibromuscular stroma. Express mesothelial markers (D2-40, WT-1, Calretinin).

Sex cord-Stromal Tumors: Rare reports of primary granulosa cell tumors and Leydig cell tumors. All in post-menopausal women.

Adrenal Medulla and Extra-adrenal Paraganglia Tumors

Pheochromocytoma

Tumor of chromaffin cells that arises in the **adrenal medulla**.
***All* malignant, but only ~10% metastasize**

Can occur at any age, but usually older adults.
~1/2 are incidentally identified (asymptomatic)

Can make catecholamines→ hypertension→ sustained or paroxysmal symptoms→ headache, tachycardia, palpitations, sweating
Can detect with urine or serum metanephrine testing

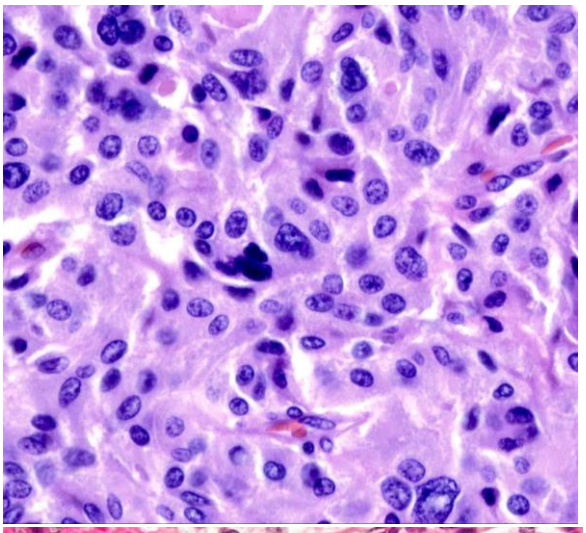
Classically, nested ("Zellballen") architecture
Can have trabecular or diffuse growth
Polygonal tumor cells with **amphophilic to purple cytoplasm**
Variable small to large nuclei
Rich vascularity→ often hemorrhage and hemosiderin
Frequent intranuclear pseudoinclusions and intracytoplasmic hyaline globules (PASD+)
Nuclear pleomorphism can be prominent, but mitoses are rare.

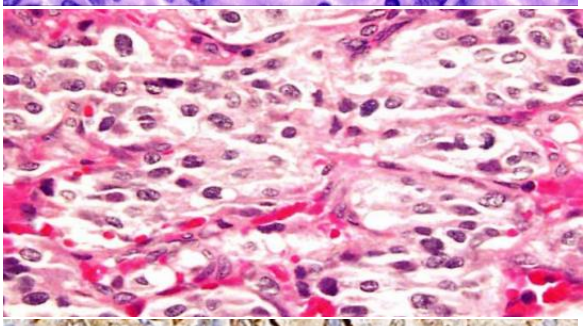
IHC: **(+) Diffuse Chromogranin** and Synaptophysin, **Sustentacular S100 and SOX10**
(-) Cytokeratins, SF1, Inhibin, Melan-A, Calretinin,

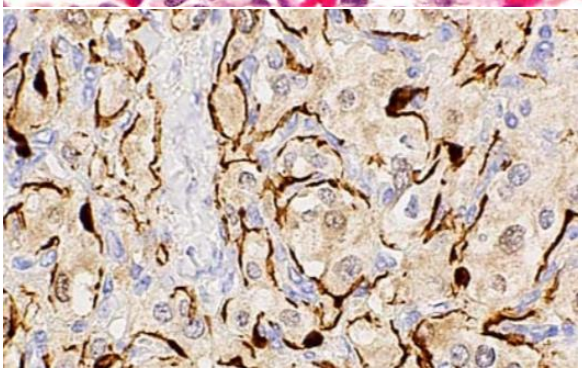
No current standardized system to assess tumor risk.

At least 30% familial due to germline mutations
The most strongly hereditary human tumor!!
Genetic testing is recommended for all patients
Common mutations: SDH, RET, NF1
SDHB mutations→ higher risk of metastases

Complete resection is only cure.
Can have metastases years later.







S100: Stains peripheral nest Sustentacular cells, highlighting *Zellballen* pattern

Paragangliomas

Arise from Extra-adrenal paraganglia, but morphologically and functionally like pheochromocytomas.
Also frequently hereditary!

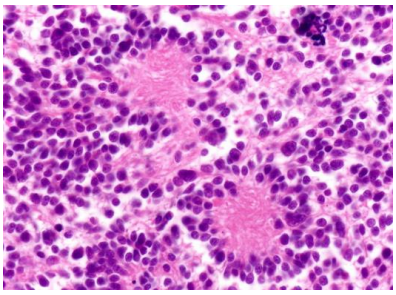
Head and Neck paragangliomas: arise from parasympathetic nerves.
Most common sites: carotid body and jugulotympanicum. Generally non-functional.
Generally good prognosis (<5% risk of metastasis)

Sympathetic paragangliomas: arise from prevertebral and paravertebral sympathetic chains and sympathetic nerves, mainly in the abdomen. Frequently functional.
Risk similar to pheochromocytomas, SDHB associated with higher risk of metastasis.

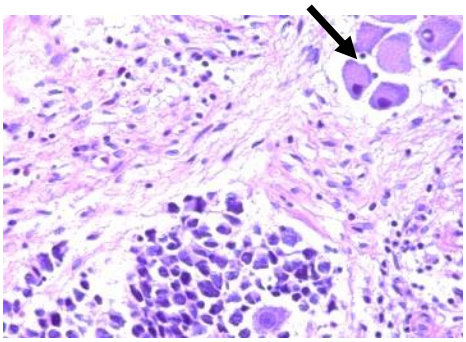
Neuroblastic Tumors

Neuroblastoma → Maturing → **Ganglioneuroblastoma** → Maturing → **Ganglioneuroma**

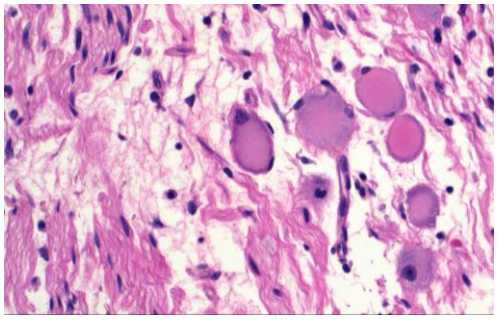
Most **primitive**/aggressive
Malignant.
Small round blue cell tumor +/- rosettes, neurofibrillary matrix. NO Schwannian stroma



Intermediate differentiation.
Malignant.
Neuroblastoma **with Schwannian stroma**, including ganglion cells



Most mature; Benign
Ganglion cells set in abundant fibrillary Schwannian stroma
NO neuroblastoma or neuropil



Derive from neural crest cells→ sites reflect path of migration→ **Most commonly in adrenal gland**, followed by abdominal ganglia, thoracic ganglia, and pelvic ganglia.

Neuroblastoma is the **3rd most common pediatric tumor** (after leukemia and brain tumors)
Most common neoplasm in the first year of life. **~90% are before age 5.**

Neuroblastoma IHC: (+) Synaptophysin, chromogranin, PGP9.5, CD56, NB84, PHOX2B
Ganglioneuroma IHC: Schwann cells (+) S100; Ganglion cells (+) Synaptophysin, neurofilament

Favorable vs Unfavorable histology is determined by age, degree of neuroblast differentiation, nodular pattern, degree of Schwannian stromal development, and mitosis-karyorrhexis- index (MKI)

Genetics: **MYCN is a major oncogenic driver. Amplification→ higher risk**
Tumors with whole-chromosome copy-number gains without structural abnormalities (hyperploidy) have an excellent prognosis

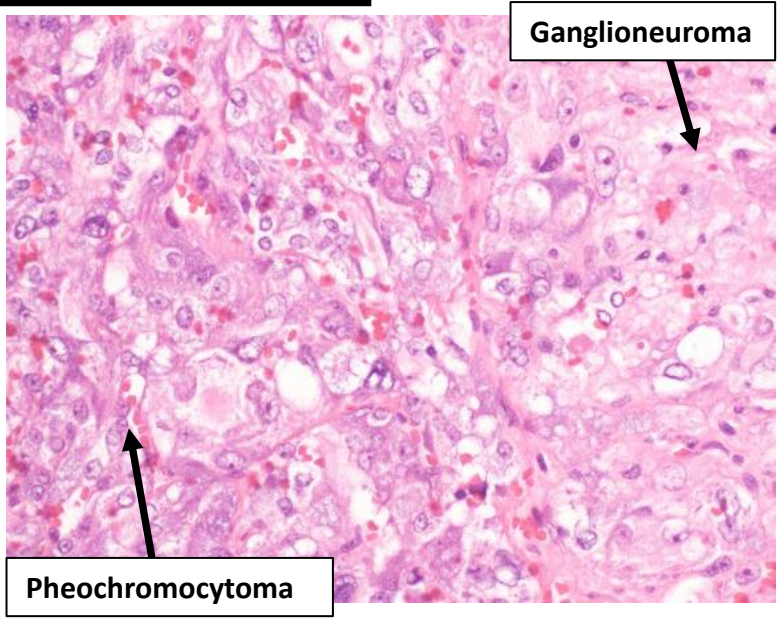
Composite Pheochromocytoma/Paraganglioma

A pheochromocytoma or paraganglioma combined with a developmentally related neurogenic tumor such as a ganglioneuroma, ganglioneuroblastoma, neuroblastoma, or peripheral nerve sheath tumor.

Each component stains/looks like it would usually.

Can occur in the setting of NF1.

If surgically resected, usually good prognosis.



Related Tumor Syndromes

Multiple Endocrine Neoplasia 1&2 (MEN)

	MEN 1	MEN 2A	MEN 2B
Gene	MEN1, autosomal dominant	RET, autosomal dominant	RET, autosomal dominant
Most common conditions	**P**arathyroid hyperplasia **P**ituitary adenoma **P**ancreatic/duodenal neuroendocrine tumors *Think "3 P's"*	Medullary thyroid carcinoma **P**arathyroid hyperplasia **P**heochromocytoma *Think "2 P's, 1 M"*	Medullary thyroid carcinoma **P**heochromocytoma Mucosal neuromas Marfanoid features *Think "1 P, 3 M's"*
Other conditions	Adrenal cortex, Thymus, lungs, stomach tumors	Hirschsprung disease	Ganglioneuromas

Often multiple tumors in each organ (e.g., diffuse pancreatic microadenomatosis with several dominant larger nodules)

Familial Paraganglioma-Pheochromocytoma Syndromes

Caused by mutations in genes encoding subunits of **Succinate dehydrogenase (SDH)**.
Autosomal dominant. Can see mutations in SDHA, SDHB (most common), SDHC, SDHD, or SDHAF2.

Most common tumor: Paraganglioma/pheochromocytoma. Can be multifocal.
Tumors associated with SDHB mutations are often more aggressive and present younger.

Other specific tumors:

SDH-deficient Gastrointestinal Stromal Tumors (GIST)—Usually occur in kids or young adults. Epithelioid morphology and can be multifocal or plexiform. Metastasize to lymph nodes, don't respond to RTK inhibitor therapy (no Ckit mutations!), but overall more indolent.

SDH-deficient Renal Cell Carcinoma (RCC)—Eosinophilic cytoplasm with "flocculent" cytoplasm/inclusions. Neuroendocrine-like nuclei (round, evenly dispersed chromatin solid to nested architecture). Young age, good prognosis.

IHC: Immunoreactivity for SDHB is *lost* in SDH-deficient tumors caused by mutations in *any* of the subunits→ can be used to screen for SDH mutations in paragangliomas, pheochromocytomas, and unusual GISTS and RCC's.

Carney Triad→ generally non-hereditary SDHC promoter hypermethylation→ Paraganglioma + SDH-deficient GIST + Pulmonary chondroma

Carney-Stratakis syndrome→ Paraganglioma + SDH-deficient GIST