Adrenal and Paraganglia Tumors

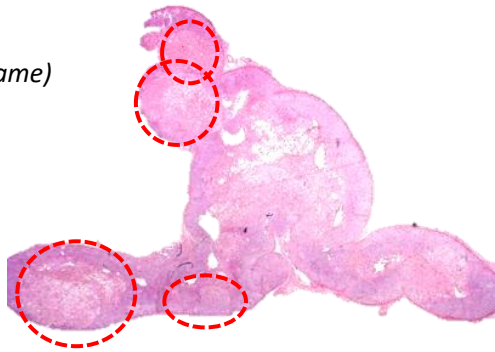
Adrenal Cortical Lesions

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

Congenital Adrenal Hyperplasia

Proliferation of cortical cells **caused by germline mutations in the enzymes used for steroid production**. Often identified by prenatal screening. May present with virilization, salt wasting, or hypertension.
Enzyme defect → ↓ hormones (no negative feedback) → ↑ACTH production → *Diffuse* adrenal hyperplasia

Adrenocortical Nodular Disease



Old name: cortical nodular hyperplasia (but can be clonal, so they changed the name)

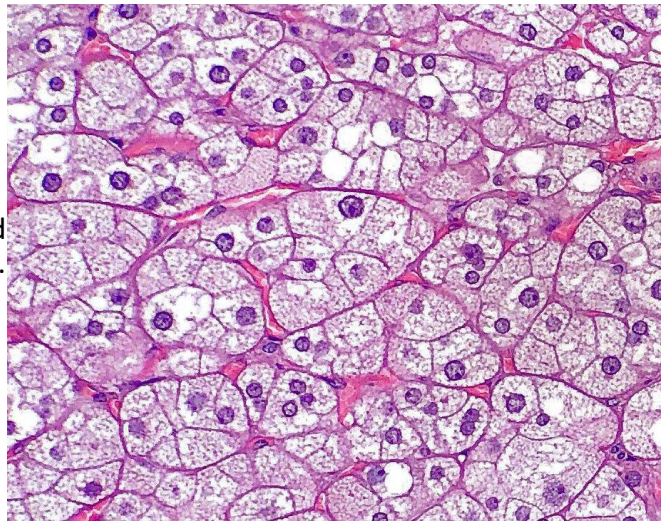
Benign adrenal cortical nodular proliferations.
May be unilateral or bilateral. Can be "sporadic" (incidental, non-functioning) or part of a mutation syndrome.

1 cm is often the dividing line between "micro" and "macro" nodules

Bilateral disease is more likely to have Cushing syndrome.

Primary Pigmented Nodular Adrenocortical Disease (PPNAD): Multiple small, pigmented nodules with intervening atrophy.

Adrenal Cortical Adenoma



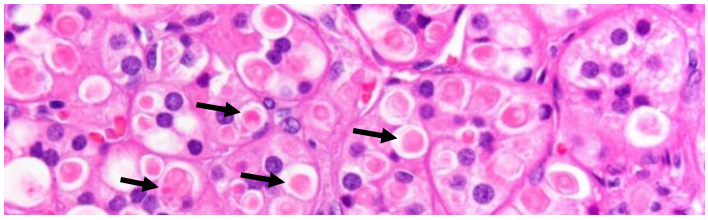
Benign. Very **common**. Often **incidentally** identified. Usually **unilateral solitary** masses with atrophic background adrenal gland. Classic "*incidentaloma*."

Tumor cells can be lipid-rich (clearer) or lipid-poor (compact, 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 nodular disease, which is more often multinodular, < 1 cm, and bilateral.

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

If aldosterone-secreting adenoma is treated with spironolactone→ "spironolactone bodies" (below)
Aldosterone-secreting tumors stain with CYP11B2 IHC



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)

Non-tumorous cortical atrophy is diagnostic of autonomous cortisol secretion in the absence of endogenous cortisol intake.

Adrenal Cortical Carcinoma

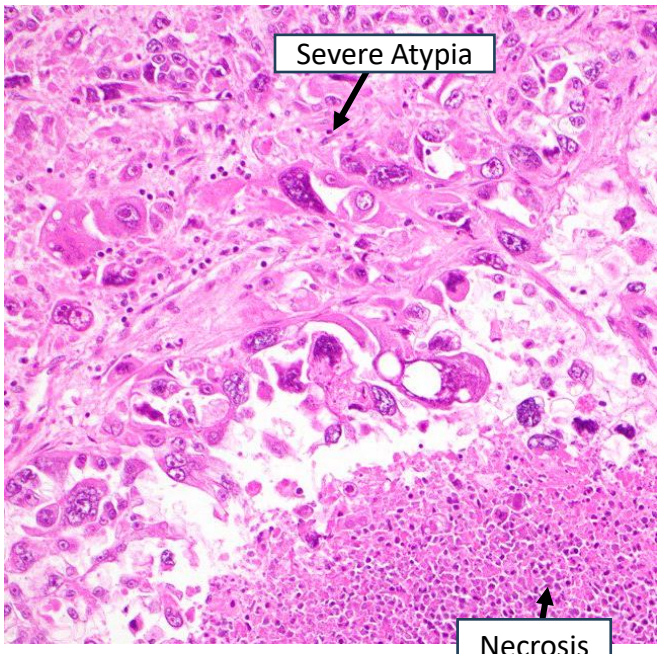
Malignant tumor of adrenal cortical cells.
Most common in older adults. Usually **unilateral**.
Usually present with mass or endocrinopathy.

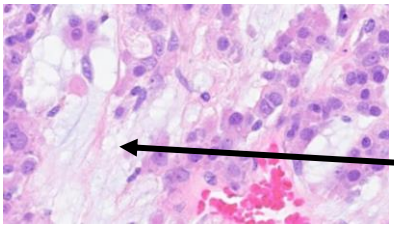
Distinguished from adenoma using multifactorial systems (see below/next page)

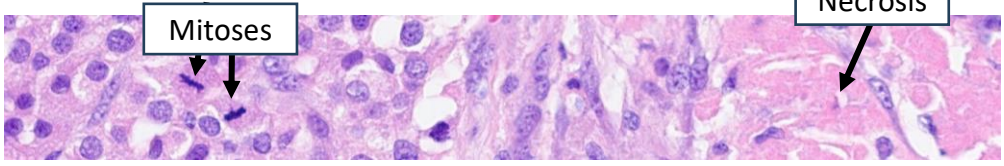
Solid, broad trabeculae, or large nested growth (more diffuse, and larger groups than in adenomas)
Thick **fibrous capsule** with occasional fibrous bands.
Frequent **tumor necrosis.**
Frequent **vascular or capsular invasion**.
Increased **mitotic activity**.

Morphology variants: Oncocytic, Myxoid, Sarcomatoid

Mostly sporadic, but can be associated syndromes







Myxoid change may obscure some findings, underestimating malignancy.

"Conventional" tumor malignancy scoring systems:

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 >30% tumor volume
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 (>5 mitotic figures/50 HPF)	2
Cytoplasm characteristics, clear vs. compact (compact, pink >75% of cells)	2
Abnormal mitoses	1
Tumor necrosis	1
Invasion of capsule	1

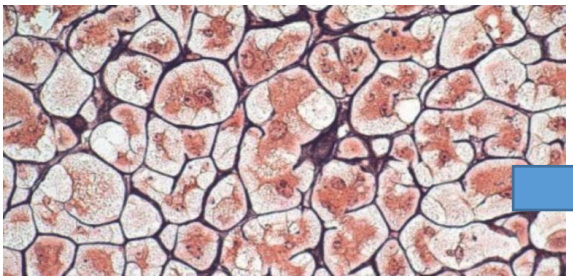
≥3 = Malignant

Adrenal Cortical Adenoma vs Carcinoma *(continued)*

Reticulin Algorithm:

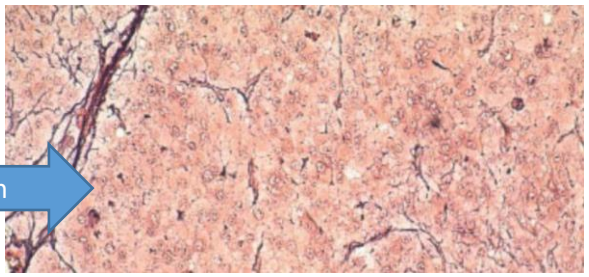
1) Look to see if reticulin framework is intact. If intact throughout→ adenoma, if disrupted, move to step 2.
2) Malignancy is defined by at least one of the following: tumor necrosis, high mitotic rate (>5/50 HPF), and venous invasion. [PMID: 23774167]

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 most systems, Ki-67 can also be helpful with this distinction.
The proliferation index in adenomas generally <5%, whereas carcinomas have a proliferation index >5%. (In kids, this threshold is often increased to 15%)

IGF2 paranuclear immunoreactivity is higher in carcinoma (vs Adenoma) too.

Helsinki Scoring system

Parameter	Score
Mitotic count >5 mitoses / 50 HPF	3
Tumor necrosis	5
Ki67 Proliferation % (numerical value counted in hotspot)	%
Benign: 0-8.5 **Malignant: >*8.5*** *(with >17 having a particularly adverse prognosis)*	

Which system should I use? There are so many!

No system has been found to be sensitive or specific in all settings. Luckily, many tumors declare themselves as overtly malignant, providing little challenge (and in these cases the main challenge may be determining if it's adrenal in origin!). However, for those challenging tumors, the WHO doesn't recommend a single system for *conventional* tumors in adults—you can choose between a Weiss system, the reticulin algorithm, or Helsinki score. They are all options.

For Oncocytic adrenal cortical tumors: you must use the LWB system, Helsinki system, or Reticulin Algorithm.

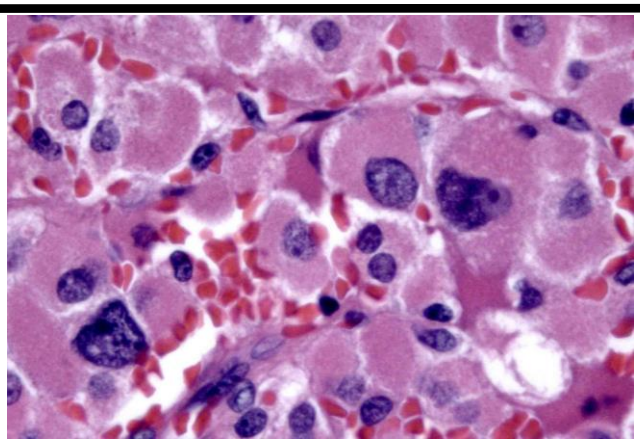
For Pediatric tumors: use the AFIP system.

Tumors with Special Systems

Oncocytic adrenocortical neoplasms (defined by **>90%** of tumor having eosinophilic cytoplasm) should not be scored using a Weiss system as it seems to overestimate malignancy risk.

Instead, use the LWB system, Helsinki score, or reticulin algorithm.

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:

1 major criteria → Malignant→ carcinoma

1-4 minor criteria →Uncertain Malignant Potential

No minor or major → Benign → adenoma

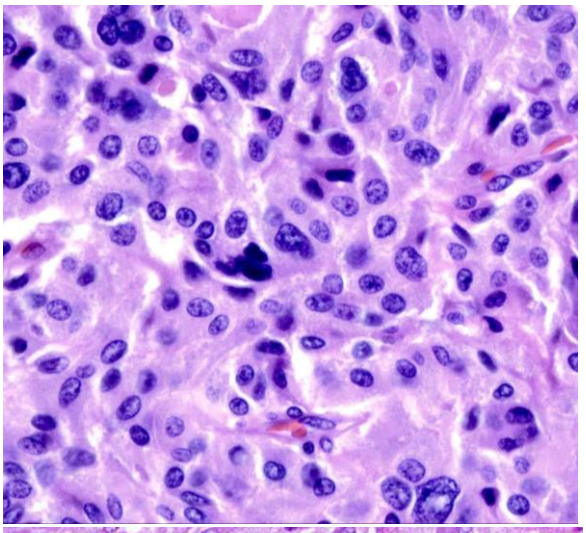
[PMID: 15306935]

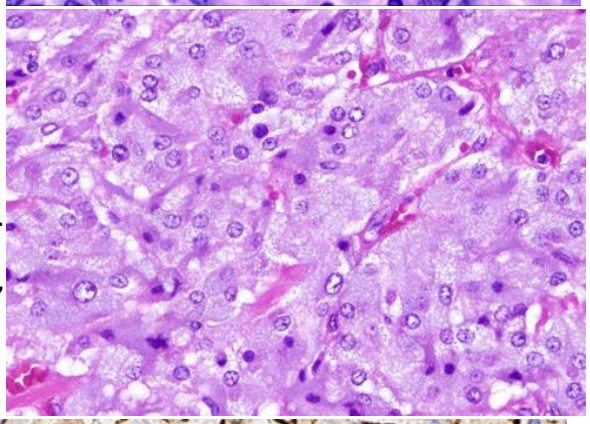
AFIP criteria for Pediatric Adrenal Cortical Neoplasms

Parameter (1 point each)
Tumor weight > 400g
Tumor size > 105mm
Extension into periadrenal soft tissue or adjacent organs
Invasion into vena cava
Vascular invasion
Capsular invasion
Presence of tumor necrosis
Mitotic count > 15 / 20 HPF
Presence of atypical mitoses
≥4 → Malignant/poor outcome **3 → Uncertain malignant potential** **≤2 → Benign**

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

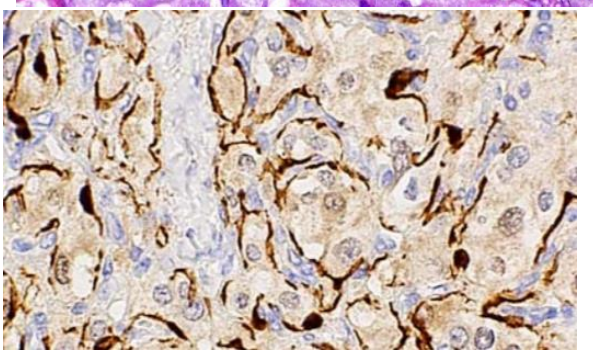
Classically, nested ("Zellballen," cell ball) architecture
Can have trabecular or diffuse growth
Polygonal tumor cells with **amphophilic to purple cytoplasm**
Variable small to large nuclei
Rich vascularity→ often hemorrhage and hemosiderin
Frequent intranuclear pseudoinclusions and intracytoplasmic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

IHC: **(+) Diffuse Chromogranin,** Synaptophysin, GATA-3, ISNM1, Tyrosine hydroxylase. **Sustentacular S100 and SOX10**
(-) Cytokeratins, SF1, Inhibin, Melan-A, Calretinin.
Useful to report Ki67 proliferation index (usually <10%)

No current standardized system to assess tumor risk.

At least 40% familial due to germline mutations
The most strongly hereditary human tumor!!
Genetic testing is recommended for all patients
Common mutations: SDH, RET, NF1, VHL,
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!

Parasympathetic (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.

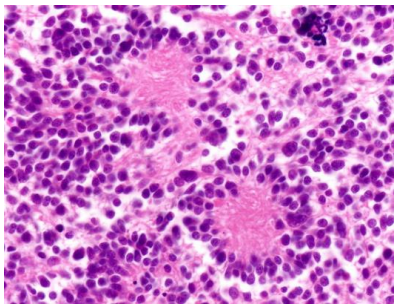
Neuroblastic Tumors

Usually in <u>infants</u>/kids.

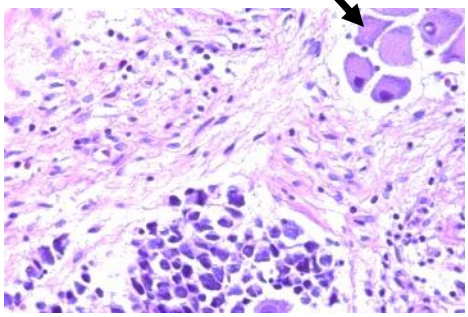
Derive from neural crest cells→ sites reflect path of migration→ **Most commonly in adrenal gland**, followed by abdominal ganglia, thoracic ganglia, and pelvic ganglia.

Neuroblastoma → Maturing → Ganglioneuroblastoma → Maturing → Ganglioneuroma

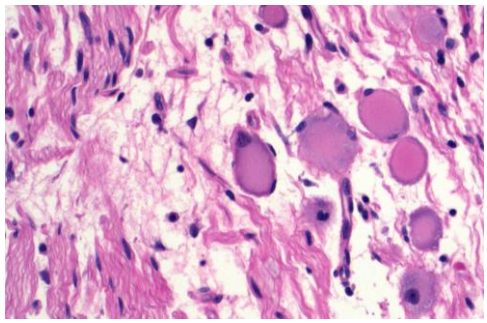
Most **primitive**/aggressive **Malignant**.
Small round blue cell tumor +/- rosettes, neuropil.
Schwannian stroma <u>poor</u>



Intermediate differentiation.
Variable risk.
Neuroblastoma **<u>with</u> rich Schwannian stroma**, including ganglion cells



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



Category	Definition	Subtype	Remarks
Neuroblastoma (Schwannian stroma-poor)	Cellular neuroblastic tumor with *<u>NO</u>* prominent Schwannian stroma	Undifferentiated	No clearly identifiable neuropil formation. (Requires IHC to prove neuroblastoma)
		Poorly-differentiated	Characteristic neuropil present. Differentiating neuroblasts <5%.
		Differentiating	Usually abundant neuropil. Differentiating neuroblasts >5%.
Ganglioneuroblastoma, intermixed (Schwannian stroma-rich)	Intermingled microscopic foci of neuroblastic elements in an expanding Schwannian stroma, constituting >50% of the tumor volume		Neuroblastic foci are microscopic, without gross nodule formation. Neuroblastic foci are composed of a mixture of neuroblastic cells in various stages of differentiation, in a background of naked neuropil.
Ganglioneuroblastoma, nodular (composite Schwannian stroma-rich/dominant and Schwannian stroma-poor)	A grossly visible neuroblastic nodular (stroma-poor) component coexisting with an intermixed Ganglioneuroblastoma (stroma-rich) or ganglioneuroma (stroma dominant) component		The proportion of components varies. The stroma-poor component is usually hemorrhagic or necrotic.
Ganglioneuroma (Schwannian stroma—dominant)	Predominantly composed of Schwannian stroma, with individually distributed neuronal elements. No detectable naked neuropil	Maturing	Contains both maturing and mature ganglion cells.
		Mature	Contains exclusively mature ganglion cells surrounded by satellite cells.

Modified from: WHO classification of tumors. Endocrine and Neuroendocrine Tumors. 5th edition. 20205.

Neuroblastoma

Peripheral neuroblastic tumor of neural crest origin.

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

Proliferating cells with variable neuroblastic differentiation.
Often grow in **nests/groups** with thin fibrovascular septa.
Salt-and-pepper nuclei. Sometimes nucleoli.
Homer-Wright rosette formation.
By definition, <50% Schwannian stroma (if >50%→ Ganglioneuroblastoma)

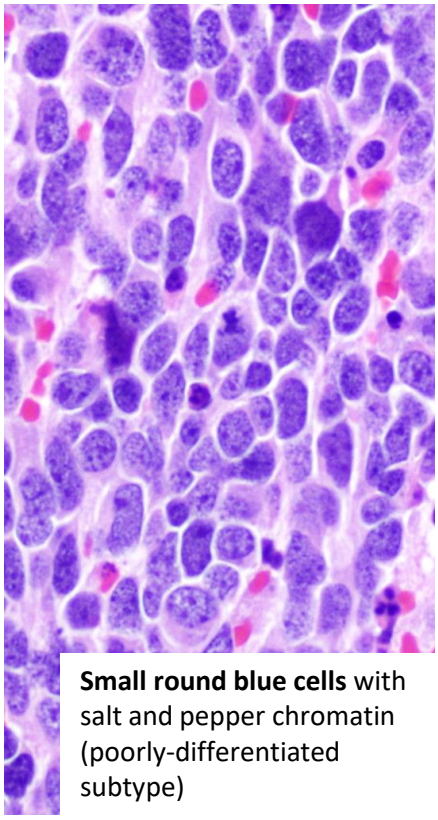
IHC: **(+) Neuroendocrine markers** (Synaptophysin, chromogranin, PGP9.5, CD56, NB84) **and Neural Crest markers** (Tyrosine hydroxylase, PHOX2B). PHOX2B is considered the most reliable marker.

For primary diagnosis→ best to use a panel to rule out other small round blue cells tumors (like rhabdomyosarcoma, etc..)

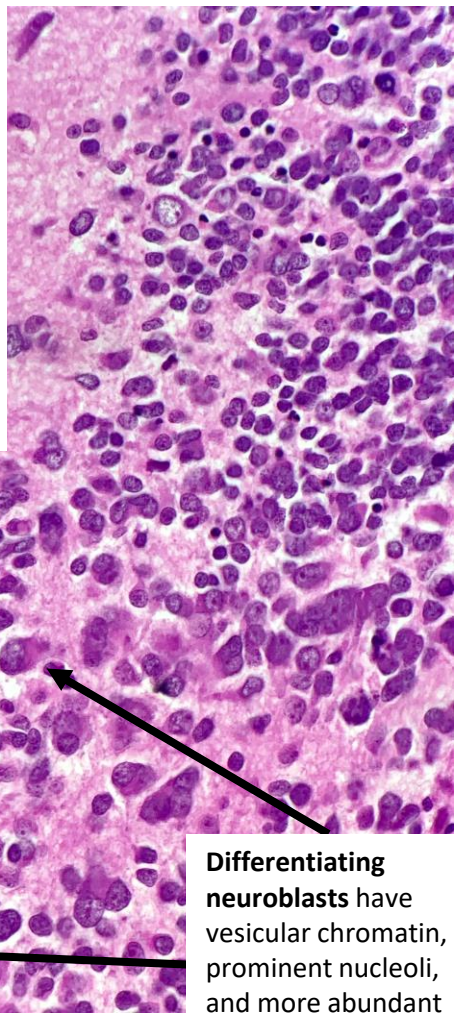
Variable **paraneoplastic syndromes,** including neurologic deficits, hypertension, and electrolyte abnormalities, through variable mechanisms including secretion and autoimmune stimulation.

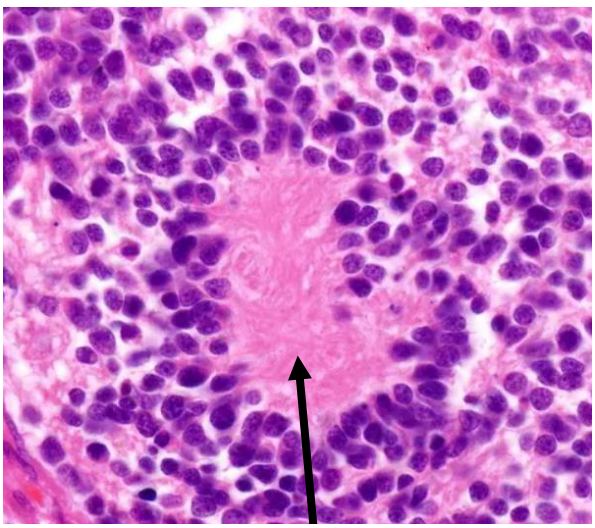
Favorable vs Unfavorable histology is determined by age, degree of neuroblast differentiation, nodular pattern, degree of Schwannian stromal development, and mitosis-karyorrhexis- index (MKI)
(I recommend referring to the CAP protocol, or similar resource, for full subtyping and risk stratification).

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



Small round blue cells with salt and pepper chromatin (poorly-differentiated subtype)

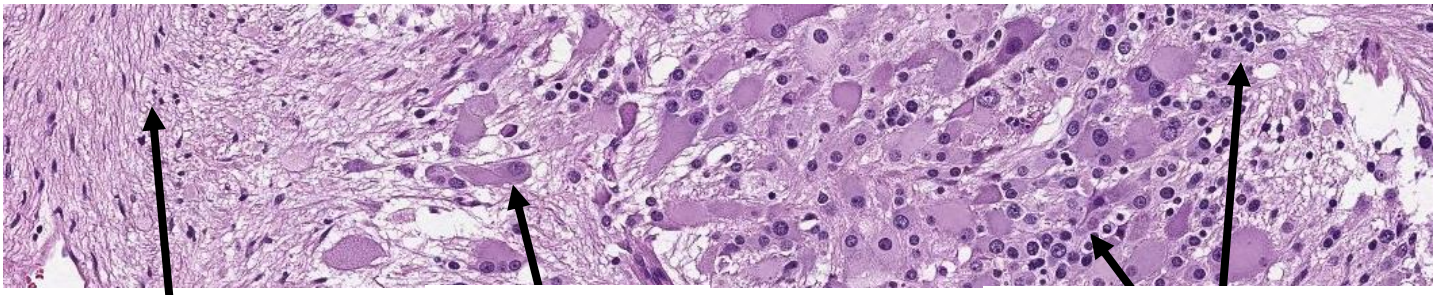




Homer-Wright **Rossette**: tumor cells around central neurofibrillary processes (neuropil).

Ganglioneuroblastoma, Intermixed

Transition from Neuroblastoma to Ganglioneuroma (same clone, intermixed with one another)
Schwannian stroma-prominent. Well-demarcated microscopic foci of neuropil and mainly differentiating neuroblastic cells. Ganlgioneuromatous component >50% of tumor volume.
Often older children (~5 yrs). Low-risk, locoregional tumor (metastases extremely rare)



Schwannian Stroma

Ganglion cells

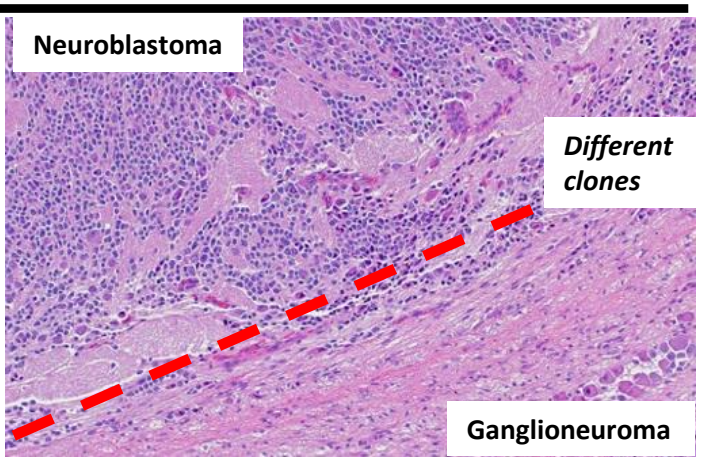
Neuroblastic cells
(neuropil not prominent in this pic)

Ganglioneuroblastoma, Nodular

Distinct, separate clones of neuroblastoma and Ganglioneuroblastoma/Ganglioneuroma.

Often <u>grossly discrete nodule</u>(s)

Assess neuroblastoma component as you would pure neuroblastoma (with MKI assessment, MYCN, etc…)



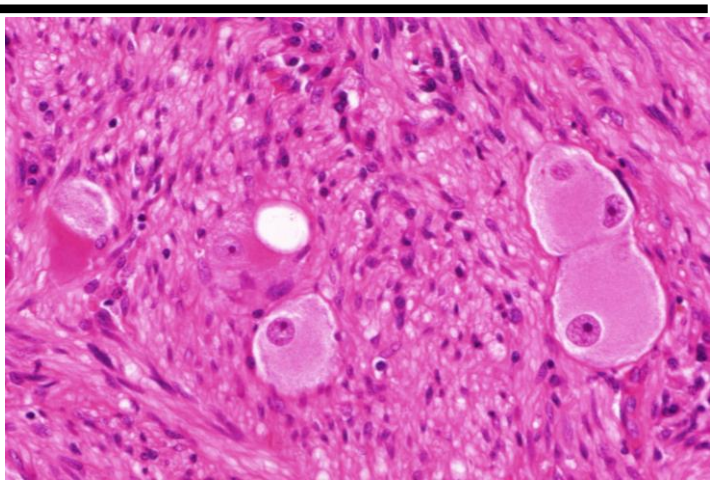
Ganglioneuroma

A dominant **Schwannian stromal component**.
Mature (or maturing) **Ganglion cells**.

<u>*No*</u> neuroblast clusters in neuropil or neuroblastoma nodules.

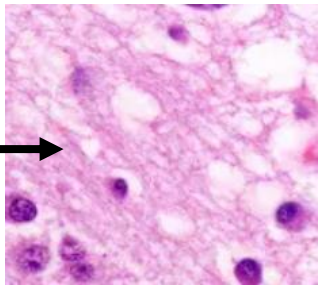
Benign. Usually incidental mass.

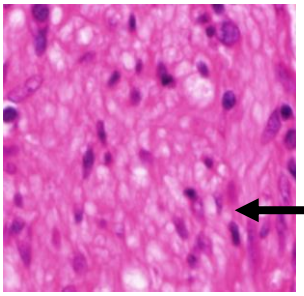
IHC: Schwann cells (+) S100;
Ganglion cells (+) Synaptophysin, neurofilament, calretinin.



<u>Neuropil</u>
Unmyelinated, naked neural dendrites
Finely textured pink fluff →
IHC: (+) Synaptophysin

Mimics: Necrosis, fibrin





<u>Schwannian Stroma</u>
Schwann cells in sheets and fascicles organized and bundled by perineurial cells.
IHC: (+) S100

Other Lesions

Adrenal cysts

Benign, circumscribed, fluid-containing.
Usually asymptomatic/incidental.

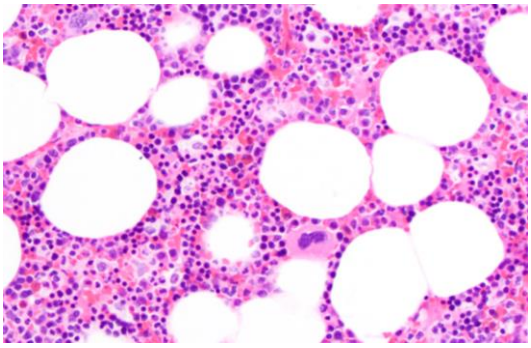
Types:
Pseudocyst—no cyst lining; hemorrhagic cyst contents
Epithelial (mesothelial) cyst—lined by mesothelial cells
Endothelial (vascular) cyst—lined by endothelium
Parasitic cyst—usually due to Echinococcus

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, but can see elsewhere, esp. in pre-sacral region.

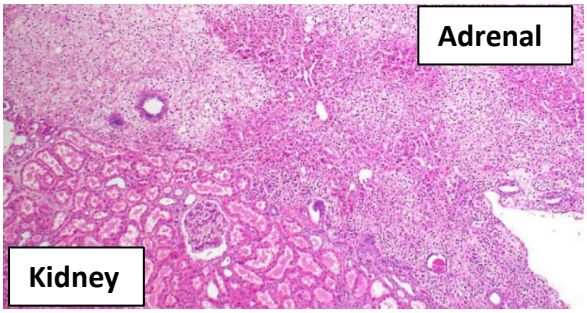


Adrenal Rests

Isolated, benign, ectopic adrenal tissue. Usually incidental. (Looks normal, just outside normal area)

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).



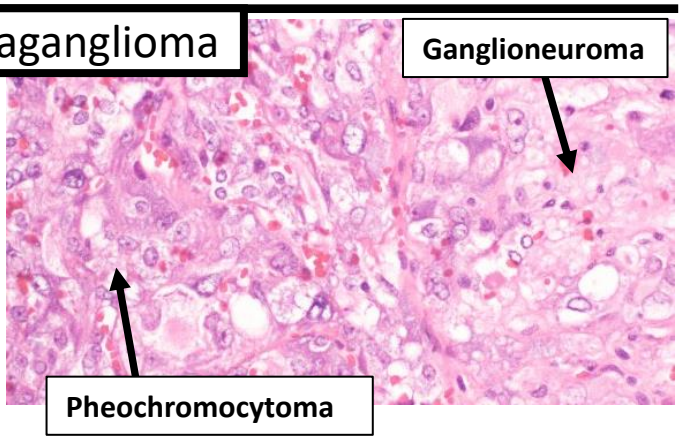
Composite Pheochromocytoma/Paraganglioma

A pheochromocytoma or paraganglioma combined with a developmentally related neurogenic tumor such as a ganglioneuroma, ganglioneuroblastoma, neuroblastoma, or peripheral nerve sheath tumor. Each must be at least 5%.

Each component stains/looks like it would usually.

Can occur in the setting of NF1.

If surgically resected, usually good prognosis.



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 Melanoma: Just like in the CNS, you can have primary adrenal melanoma. This is a diagnosis of exclusion though and you must exclude a metastasis!

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: <u>Paraganglioma/pheochromocytoma</u>. Can be multifocal.
Tumors associated with SDHB mutations are often more aggressive and present younger.

Other specific tumors:

<u>SDH-deficient Gastrointestinal Stromal Tumors (GIST)</u>—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.

<u>SDH-deficient Renal Cell Carcinoma (RCC)</u>—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 *<u>lost</u>* in SDH-deficient tumors caused by mutations in *<u>any</u>* 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