Adrenal and Paraganglia Tumors

Adrenal Cortical Tumors

**Adrenal Cortical Adenoma**


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)

**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

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

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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)
Distinguishing between an Adrenal Cortical Adenoma vs Carcinoma

<table>
<thead>
<tr>
<th>Weiss Criteria (≥3 = Malignant)</th>
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<tbody>
<tr>
<td>High nuclear grade (based of Fuhrman criteria)</td>
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<tr>
<td>Mitotic rate of &gt;5 mitoses per 50 HPF</td>
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<tr>
<td>Atypical mitotic figures</td>
</tr>
<tr>
<td>&lt;25% Clear cells</td>
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<tr>
<td>Diffuse architecture</td>
</tr>
<tr>
<td>Tumor necrosis</td>
</tr>
<tr>
<td>Venous invasion</td>
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<tr>
<td>Sinusoidal invasion</td>
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<td>Capsular invasion</td>
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**Weiss Criteria:**
Most widely used system, but doesn’t work as well in borderline cases or variants. The presence of ≥3 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: 23774167]

**“Modified” Weiss Criteria:**
Designed to be more reproducible.
Total score of 3 or greater correlates with subsequent malignant behavior

[PMID: 12459628]

**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]

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).

<table>
<thead>
<tr>
<th>Lin-Weiss-Bisceglia Criteria:</th>
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<tbody>
<tr>
<td><strong>Major Criteria</strong></td>
</tr>
<tr>
<td>Mitotic rate &gt;5 per 50 HPF</td>
</tr>
<tr>
<td>Atypical mitotic figures</td>
</tr>
<tr>
<td>Venous invasion</td>
</tr>
<tr>
<td><strong>Minor Criteria</strong></td>
</tr>
<tr>
<td>Size &gt;10 cm and/or weight &gt;200 g</td>
</tr>
<tr>
<td>Tumor necrosis</td>
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<td>Sinusoidal invasion</td>
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<td>Capsular invasion</td>
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</table>

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.
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.

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)


Risk similar to pheochromocytomas, SDHB associated with higher risk of metastasis.
**Neuroblastic Tumors**

<table>
<thead>
<tr>
<th>Neuroblastoma</th>
<th>Maturing</th>
<th>Ganglioneuroblastoma</th>
<th>Maturing</th>
<th>Ganglioneuroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most primitive/aggressive Malignant.</td>
<td>Small round blue cell tumor +/- rosettes, neurofibrillary matrix. NO Schwannian stroma</td>
<td>Intermediate differentiation. Malignant. Neuroblastoma with Schwannian stroma, including ganglion cells</td>
<td>Most mature; Benign Ganglion cells set in abundant fibrillar Schwannian stroma NO neuroblastoma or neuropil</td>
<td></td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>MEN 1</th>
<th>MEN 2A</th>
<th>MEN 2B</th>
</tr>
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<tbody>
<tr>
<td><strong>Gene</strong></td>
<td>MEN1, autosomal dominant</td>
<td>RET, autosomal dominant</td>
</tr>
</tbody>
</table>
| **Most common conditions** | Parathyroid hyperplasia Pituitary adenoma Pancreatic/duodenal neuroendocrine tumors  
*Think “3 P’s”* | Medullary thyroid carcinoma Parathyroid hyperplasia Pheochromocytoma  
*Think “2 P’s, 1 M”* | Medullary thyroid carcinoma Pheochromocytoma 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