Adrenal Pathology: A urological pathologist’s perspective

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Division Chief, Anatomic Pathology
University of California at San Diego
Overview

• Embryologic development and function of the adrenal gland

• Hyperplasia and dominant nodules

• Adrenal cortical carcinoma

• Pheochromocytoma

• Miscellaneous lesions that involve the adrenal gland
Embryologic development of adrenal gland

• Adrenal cortical primordia appear at Carnegie development stage 14 (33 days gestation)
  – Adrenal medulla begins formation Carnegie developmental stage 16-17 (39 days)
  – Cortisol, DHAS likely important in fetal development

• Dynamic interaction of adrenal primordium with germ cells and neural crest cells during development

• Genes include WT1, SF1, PBX1 among others
  – IGF pathway critical in adrenal cortex development

• Congenital abnormalities include congenital adrenal hyperplasia (primary adrenal insufficiency) and Beckwith-Wiedemann syndrome
# Embryologic development of adrenal gland

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Defect if absent</th>
<th>Syndrome/findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT1</td>
<td>DNA binding protein</td>
<td>Adrenal, kidney, gonad aplasia</td>
<td>WAGR; Denys-Drash; Frasier</td>
</tr>
<tr>
<td>WNT4</td>
<td>Binds frizzled; activates (\beta)-catenin</td>
<td>Lack of kidney development</td>
<td>Masculinizing</td>
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<tr>
<td>SF1</td>
<td>DNA binding protein</td>
<td>Absence of gonad, adrenal</td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>PBX1</td>
<td>DNA binding protein (HOX genes)</td>
<td>Impaired kidney differentiation</td>
<td>Adrenal agensis</td>
</tr>
</tbody>
</table>

## Adrenocortical Growth and Cancer

Lucia Leifone,1-3 Jordana Berhardt,1-4 and Bruno Ragozzino1-3

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[Diagram showing stages of embryologic development of adrenal gland and associated genes and functions.]

**Abbreviations:**
- WAGR: Wilms tumor, aniridia, genitourinary anomalies, mental retardation
- Denys-Drash Syndrome
- Frasier Syndrome
- POMC: Proopiomelanocortin
- shh: Sonic hedgehog
Abnormal localization of adrenal tissue within the GU tract

- Adrenal gland development results in occasional ectopic rests
  - Embedded with kidney (union/fusion)/ renal-adrenal adhesion
  - Heterotopic tissue in spermatic cord (up to 9%)
Adrenal gland in the adult

- 4-6 grams – no preference for side or gender
- Right gland pyramidal in shape, whereas left more elongated
- Medulla occupies approximately 10% of the volume
- Lipomatous change (5%) and ovarian thecal metaplasia (4% females) can be seen
Excess and deficiency in layers results in specific clinical findings

Zona glomerulosa (mineralocorticoids)
Aldosterone

Zona fasciculata (glucocorticoids)
Cortisol

Zona reticularis (sex steroids/androgens)

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Z glomerulosa (CYP11B2)</th>
<th>Z fasciulata (CYP17, CYP11B1)</th>
<th>Z reticularis (CYP17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>↑K, ↓Na, hypotension</td>
<td>Hypoglycemia</td>
<td>Virilization</td>
</tr>
<tr>
<td>Excess production</td>
<td>Hypertension, heart failure</td>
<td>Cushing’s syndrome</td>
<td></td>
</tr>
</tbody>
</table>
Adrenal lesions are being identified more frequently using imaging.

Table 2 Anatomic location of incidental findings
Pre- and post-IF protocol

<table>
<thead>
<tr>
<th>Findings</th>
<th>Pre-IF protocol N (% all patients)</th>
<th>Post-IF protocol N (% all patients)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any incidental finding</td>
<td>147 (20.4)</td>
<td>99 (23.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Renal lesions</td>
<td>87 (12.6)</td>
<td>59 (13.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Hepatic lesions</td>
<td>54 (7.9)</td>
<td>41 (9.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Adrenal lesions</td>
<td>25 (3.6)</td>
<td>13 (3.0)</td>
<td>0.6</td>
</tr>
<tr>
<td>Pancreatic lesions</td>
<td>6 (0.9)</td>
<td>4 (0.9)</td>
<td>0.9</td>
</tr>
<tr>
<td>Ovarian lesions</td>
<td>2 (0.3)</td>
<td>1 (0.2)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

CT imaging of 1,117 patients with trauma – incidental abdominal findings.
Categorization of adrenal “tumors” in adults

Cortex
• Adrenal cortical hyperplasia (+/- dominant nodule)
• Adrenal cortical adenoma
• Adrenal cortical carcinoma

Medulla
• Adrenal medullary hyperplasia (<1 cm)
• Pheochromocytoma
• Myelolipoma
• Vascular lesions, hemorrhage

NOS
• Infections/abscess/TB
• Metastasis
Table 1
Genetic syndromes associated with adrenal hyperplasia/neoplasia.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Heritage</th>
<th>Locus</th>
<th>Gene</th>
<th>Clinical features</th>
<th>Adrenal manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple endocrine neoplasia type 1</td>
<td>Autosomal dominant</td>
<td>11q13</td>
<td>MEN1</td>
<td>Primary hyperparathyroidism, gastric, pancreatic, and duodenal neuroendocrine tumors, pituitary adenomas, thymic carcinoid tumors</td>
<td>Non-functioning macronodular hyperplasia in up to 40% of patients. ACCs rarely described</td>
</tr>
<tr>
<td>Carney’s complex</td>
<td>Autosomal dominant</td>
<td>17q22-24</td>
<td>PRKAR1A</td>
<td>Cutaneous lentigens, pituitary adenomas, cardiac myxomas, pancreatic, and cutaneous tumors</td>
<td>Micronodular pigmented adrenal hyperplasia</td>
</tr>
<tr>
<td>McCune–Albright syndrome</td>
<td>Sporadic (post-zygotic somatic mosaicism)</td>
<td>20q13.3</td>
<td>GNAS1</td>
<td>Polysototic bone dysplasia, gonadotropin-independent precocious puberty, café-au-lait spots, pituitary adenomas</td>
<td>Cortisol-producing bilateral nodular hyperplasia</td>
</tr>
<tr>
<td>Gardner’s syndrome</td>
<td>Autosomal dominant</td>
<td>5q21-q22</td>
<td>APC</td>
<td>Familial adenomatosis polyposis, increased risk for colon cancer, thyroid tumors, osteomas of the skull</td>
<td>Bilateral adrenocortical hyperplasia in 7–13%</td>
</tr>
<tr>
<td>ACTH-independent adrenal macronodular hyperplasia (AIMAH)</td>
<td>Sporadic/autosomal dominant</td>
<td>?/ ?/</td>
<td>Overexpression of GPCRs of different classes in adrenal nodules</td>
<td>Bilateral nodular enlargement of adrenal glands associated with Cushing’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Li–Fraumeni syndrome</td>
<td>Autosomal dominant</td>
<td>17p13</td>
<td>TP53</td>
<td>Increased risk for sarcomas, hematologic malignancies, lung tumors, breast tumors</td>
<td>ACCs in 5%</td>
</tr>
<tr>
<td>Beckwith–Wiedemann syndrome</td>
<td>Autosomal dominant/sporadic</td>
<td>11p15</td>
<td>IGF2</td>
<td>Organomegaly, omphalocele, microcephaly, mental retardation, fetal neoplasms (Wilms’ tumor, hepatoblastoma, ACC)</td>
<td>ACT in 1.5%</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>Autosomal dominant</td>
<td>17q11.2</td>
<td>NF1</td>
<td>Café au lait spots, cutaneous neurofibromas, nerve sheath tumors, pheochromocytoma</td>
<td>ACTs describes in at least 4 cases, including 2 children ACC described in one case, in which AIP LOH could be verified</td>
</tr>
<tr>
<td>FIPA</td>
<td>Autosomal dominant</td>
<td>11q13.3</td>
<td>AIP</td>
<td>Familial pituitary tumors (somatotropinomas)</td>
<td>AIP inactivation leads to abnormal PKA activity;</td>
</tr>
</tbody>
</table>

The high frequency of 11q LOH suggests a potential role in the pathogenesis of adrenal hyperplasia.
Adrenal cortical hyperplasia

• Non-neoplastic process
  – Genetic syndromes and Cushing’s disease

• Increased number of cells in the cortex

• Multiple “subtypes”
  – Diffuse (thickened; occasional small nodules)
  – Micronodular (<0.5 or 1.0 cm) and macronodular (>1.0 cm nodules)
  – Mixed

• Commonly a bilateral process

• Occasionally may have pigment

• Size and weight may be helpful in subtle cases
Clinical endocrine syndromes associated with hyperplasia

**Hyperaldosteronism**
Associated most commonly with adenoma

- Hyperkalemia, hypertension

**Cushing’s syndrome**
Cushing’s disease (pituitary)
Ectopic ACTH production (paraneoplastic)
Macronodular adrenal hyperplasia (mutations of armadillo repeat containing 5 gene in familial cases; APC, MEN1)
Micronodular adrenal hyperplasia (excess cAMP signaling)

- Abdominal obesity, round facies, red striae, acne, fat between shoulders

**Virilization**
Adrenal hyperplasia
Micronodular hyperplasia
Macronodular hyperplasia
Dominant nodule associated with hyperplasia
Hyperplasia versus adenoma

Hyperplasia/dominant nodule favored by:
  Bilaterality (imaging)
  Background of hyperplasia

Adenoma favored by:
  Unilateral process (imaging)
  Background of atrophic adrenal gland
Adrenal cortical adenoma

• Benign neoplasm derived from cortical cells
  – More common in women; incidence same in right and left adrenals

• Functional or non-functional in nature (clinical) - 15%
  – Clinical history and syndromes are helpful

• Non-functional adenomas discovered incidentally - 85%

• Functional adenomas associated with:
  – Primary hyperaldosteronism
  – Cushing’s syndrome
  – Virilization or feminization

• Often confusion with adrenal macronodule
  – Solitary lesion in an non-hyperplastic or atrophic adrenal background most helpful to diagnosis adenoma

• May have degenerative features (cystic change, sclerosis)
Immunomarkers to distinguish cortical tissue

Positive markers
  - Inhibin
  - Calretinin
  - Melan-A
  - Synaptophysin

Negative markers
  - Epithelial markers generally negative
  - Chromogranin
  - S100
Variants of adrenal adenoma

- Classic
- Pigmented
  - intracytoplasmic lipofuscin
  - may be functional (Cushing)
- Oncocytic
  - usually nonfunctional
  - abundant mitochondria
- Myxoid
  - extracellular mucin
  - pseudoacinar
Cortical adenoma
Adrenal cortical adenoma with lipid rich cells and trabecular architecture
Adrenal cortical adenoma with lipid rich and lipid poor cells
Adrenal cortical adenoma with lipid poor cells and a sinusoidal architecture
Adrenal cortical adenoma with lipid poor cells and a tubular architecture
Pigmented Adrenal Cortical Adenoma
Oncocytic adrenal cortical adenoma
Myxoid features
Adrenocortical carcinoma

• Malignant neoplasm arising from cortical cells

• Affects 1-2 people/million
  – Often adults in the 30s and 40s
  – Subset affects pediatric population as well
  – Risk with Beckwith-Widemann and Li-Fraumeni syndromes

• No clear cut gender or race predilection

• Left side affected slightly more commonly

• May be functioning (pure or mixed) or non-functioning

• Metastasis occurs to bilateral gland, lung, bone, mediastinum, other
Gross findings

• Usually large tumors (hundreds to thousands of grams)
  – >95 grams often carcinoma
  – Average weight 510-1210 grams
  – Larger weight may mean worse prognosis
  – Large adrenal tumors may be ACC (44%), mets (27%) or pheochromocytomas (21%); [Mege et al; Anticancer Res]

• Irregularly lobulated
  – Fibrous bands often present

• Yellow-orange to tan in appearance

• Necrosis common
Defining outcomes in adrenocortical carcinoma

• Weiss criteria (1984)

• 43 tumors (metastasizing, non-metastasizing)
  – Nine criteria
    • Nuclear grade III or IV
    • Mitotic rate > 5/50 HPF
    • Atypical mitoses
    • Clear cells ≤25% of tumor
    • Diffuse architecture
    • Microscopic necrosis
    • Invasion of vein or capsule
  – Most of the 19 that recurrent or metastasized had 4 or more of these criteria
  – Mitotic activity (especially atypical) and venous invasion correlated best with metastasis or recurrence
Weiss System Revisited
A Clinicopathologic and Immunohistochemical Study of 49 Adrenocortical Tumors

Sébastien Aubert, M.D., Agnès Wacrenier, M.D., Xavier Leroy, M.D., Patrick Devos, Bruno Carnaille, M.D., Charles Proye, M.D., Jean Louis Wemeau, M.D., Martine Lecomte-Houcke, M.D., and Emmanuelle Leteurtre, M.D.

Score of 0 to 7:
>5 mits/50 HPF (2)
≤ 25% clear tumor cells (2)
Abnormal mitoses (1)
Necrosis (1)
Capsular invasion (1)

≥ 3 indicates malignant behavior
r=0.94
Sensitivity 100%, specificity 96%

Helsinki score

3 x mitotic rate + 5 x necrosis + PI %

Fig. 1  A to D, The Helsinki score: 3 x mitotic rate greater than 5/50 high-power fields + presence of necrosis + PI. C, Ki-67 staining. D, immunohistochemical pseudocolor image of Ki-67 staining. HE and IHC images, original magnification x400.
## Significantly mutated genes (TCGA)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>ZFPM1</td>
<td>zinc finger protein, multitype 1</td>
</tr>
<tr>
<td>LACTB</td>
<td>beta lactamase</td>
</tr>
<tr>
<td>CCDC102A</td>
<td>coiled-coil domain containing 102A</td>
</tr>
<tr>
<td>ZNF517</td>
<td>zinc finger protein 517</td>
</tr>
<tr>
<td>TOR3A</td>
<td>torsin family 3, member A</td>
</tr>
<tr>
<td>USP42</td>
<td>ubiquitin specific peptidase 42</td>
</tr>
<tr>
<td>CLDN23</td>
<td>claudin 23</td>
</tr>
<tr>
<td>TP53</td>
<td>tumor protein p53</td>
</tr>
<tr>
<td>KCNK17</td>
<td>potassium channel, subfamily K, member 17</td>
</tr>
<tr>
<td>LZTR1</td>
<td>leucine-zipper-like transcription regulator 1</td>
</tr>
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</table>
**Pheochromocytoma**

- Paraganglioma derived from chromaffin cells in the adrenal medulla

- 8 cases/million annually
  - Right side involved slightly more often
  - No gender predilection
  - Any age group, but often 40s

- If symptoms present, commonly include hypertension, tachycardia or postural hypotension
  - Check blood and urine catecholamine levels

- “10 percent tumor”
  - Bilateral, extraadrenal, malignant, occurring in childhood

- Can be sporadic or syndromic
  - MEN2a and 2b association (often bilateral or multifocal)
  - Carney’s triad
Gross findings

- Solitary mass
- May overtake background adrenal gland
- 3-5 cm on average
- Malignant tumors tend to be larger
- No true capsule (fibrous pseudocapsule)
- Firm, grey-white to mottled and hemorrhagic
- Can extend into the inferior vena cava and right atrium
Pigmented Pheochromocytoma
Synaptophysin

Inhibin
Scoring of pheochromocytomas

- Pheochromocytoma of the Adrenal Gland Scaled Score (PASS)
- 50 malignant and 50 benign tumors

- Score of ≥4 suggestive of aggressive behavior
  - Vascular invasion (1)
  - Capsular invasion (1)
  - Periadrenal adipose tissue (2)
  - Large nests or diffuse growth (2)
  - Focal or confluent necrosis (2)
  - High cellularity (2)
  - Tumor cell spindling (2)
  - Cellular monotony (2)
  - >3 mitoses/10 HPF (2)
  - Atypical mitotic figures (2)
  - Profound nuclear pelomorphism (1)
  - Hyperchromasia (1)
Pathological grading for predicting metastasis in phaeochromocytoma and paraganglioma

Noriko Kimura, Ryoichi Takayanagi, Naetokizawa, Eiji Itagaki, Takayuki Katabami, Narihiko Kakoi, Hiromi Rakugi, Yukihiro Ikeda, Akiyo Tanabe, Takeshi Nigawara, Sadayoshi Ito, Itaru Kimura, Mitsuhide Naruse and The Phaeochromocytoma Study Group in Japan

Table 1  GAPP parameters and scoring point

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Points scored</th>
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<tbody>
<tr>
<td>Histological pattern</td>
<td></td>
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<tr>
<td>Zellballen</td>
<td>0</td>
</tr>
<tr>
<td>Large and irregular cell nest</td>
<td>1</td>
</tr>
<tr>
<td>Pseudorosette (even focal)</td>
<td>1</td>
</tr>
<tr>
<td>Cellularity</td>
<td></td>
</tr>
<tr>
<td>Low (&lt;150 cells/U)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate (150–250 cells/U)</td>
<td>1</td>
</tr>
<tr>
<td>High (more than 250 cells/U)</td>
<td>2</td>
</tr>
<tr>
<td>Comedo necrosis</td>
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<tr>
<td>Absence</td>
<td>0</td>
</tr>
<tr>
<td>Presence</td>
<td>2</td>
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<tr>
<td>Vascular or capsular invasion</td>
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<tr>
<td>Absence</td>
<td>0</td>
</tr>
<tr>
<td>Presence</td>
<td>1</td>
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<tr>
<td>Ki67 labelling index (%)</td>
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</tr>
<tr>
<td>&lt;1</td>
<td>0</td>
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<tr>
<td>1–3</td>
<td>1</td>
</tr>
<tr>
<td>&gt;3</td>
<td>2</td>
</tr>
<tr>
<td>Catecholamine type</td>
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<tr>
<td>Epinephrine type (E or E + NE)</td>
<td>0</td>
</tr>
<tr>
<td>Norepinephrine type (NE or NE + DA)</td>
<td>1</td>
</tr>
<tr>
<td>Non-functioning type</td>
<td>0</td>
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<tr>
<td>Total maximum score</td>
<td>10</td>
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</table>
Molecular pathogenesis of pheochromocytoma

Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity

Patricia L. M. Dahia

Abstract: The neuroendocrine tumours pheochromocytomas and paragangliomas carry the...
HIF activation characterizes a subset of pheochromocytomas
High-Throughput Screening for the Identification of New Therapeutic Options for Metastatic Pheochromocytoma and Paraganglioma

Alessio Giubbellino1, Uma Shankavaram5, Petra Bullova1,6, Jan Schovanek1,7, Yaqin Zhang2, Min Shen2, Nikita Patel1, Abdel Elkahloun3, Min-Jung Lee4, Jane Trepel4, Marc Ferrer2, Karel Pacák1

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A

<table>
<thead>
<tr>
<th>Compound</th>
<th>Correlation Index</th>
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<tbody>
<tr>
<td>Bortezomib</td>
<td>3</td>
</tr>
<tr>
<td>Lestauntinib</td>
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</tr>
<tr>
<td>Zinc pyrithione</td>
<td>114</td>
</tr>
<tr>
<td>Pyrithione</td>
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<tr>
<td>SAHA</td>
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<tr>
<td>Flavopiridol</td>
<td>797</td>
</tr>
<tr>
<td>17-AAG</td>
<td>303</td>
</tr>
<tr>
<td>Colchicine</td>
<td>352</td>
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<tr>
<td>Rubitecan</td>
<td>225</td>
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<tr>
<td>Carubicinum</td>
<td>173</td>
</tr>
<tr>
<td>Phenelzine sulfate</td>
<td>6</td>
</tr>
</tbody>
</table>

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B

Correlation Index (murine MTT cells vs human SDHB PGL)
Metastatic lesions involving the adrenal

- Often seen in the context of clear cell renal cell carcinoma
- Metastases will most often mimic adrenocortical carcinoma
- Precedent history may be absent or primary tumor unrecognized
Metastatic clear cell renal cell carcinoma
Cytokeratin

Inhibin
Desmoplasia

S100
Miscellaneous lesions involving the adrenal gland

Hemorrhage

Thrombus

Myelolipoma
Summary

• Major differential diagnostic categories often require clinical and radiographic correlation
  – Blood/urine test results in pheochromocytoma
  – Imaging findings of bilaterality
  – Syndromes

• Scoring paradigms have been suggested for adrenocortical carcinoma and pheochromocytoma
  – Supporting studies but some disagreement and refinements
  – Molecular paradigms and proteomic analysis may modify these paradigms

• Metastatic lesions can be important mimickers of adrenal lesions, especially adrenocortical carcinoma