DISEASES OF ADRENAL GLAND-1

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HYPERCORTISOLISM

- AKA Cushing syndrome
- Can be exogenous (iatrogenic) or endogenous (less common)
- Endogenous causes are divided into ACTH-dependent and indepedendent
- **ACTH-secreting PA** is the most common cause of endogenous hypercorticolism (60%), AKA Cushing Disease, more common in women, young adults, functional microadenoma
- In rare cases, corticotroph hyperplasia (excessive CRH secretion from hypothalamic tumor)
- Adrenal glands show bilateral nodular hyperplasia

HYPERCORTISOLISM

- **Ectopic ACTH production:**
- 5-10% of endogenous Cushing syndrome cases
- More common in men, middle age
- Small cell carcinoma of lung, carcinoid tumor, medullary carcinoma of thyroid, pancreatic neuroendocrine tumors
- In some cases, ectopic production of CRH
- Again, bilateral adrenal nodular hyperplasia
- Pathologic changes is less prominent than pituitary cause, secondary to poor prognosis of accompanied cancer

HYPERCORTISOLISM

- **Primary adrenal adenoma**
- 10-20% of ACTH-independent cases
- Low ACTH level (negative feedback on pituitary)
- PRKAR1A genetic mutation
- The other adrenal gland is atrophic

HYPERCORTISOLISM

- **Adrenal carcinoma**
- 5-7% of ACTH-independent cases
- Very large size of adrenal glands
- Produces very high level of cortisol
- Genetic mutations in: activation of beta-catenin (CTNNB1), inactivation of TP53, MEN1 and PRKAR1A
- The other adrenal gland is atrophic

HYPERCORTISOLISM

- Primary adrenal hyperplasia:
- Independent of ACTH
- Rare
- Shows bilateral adrenal cortical hyperplasia, nodules are larger than 1 cm
- Familial disease: inherited mutation in the tumor suppressor gene: armadillo repeat containing 5 (ARMC5)
- Sporadic disease: 50% show ARNC5 mutation, others show ectopic production of G-protein coupled hormone receptors (similar action of ACTH)
- Syndromic disease: McCune Albright syndrome, germline activating mutation in GNAS, produces excessive cAMP → multisystemic disease

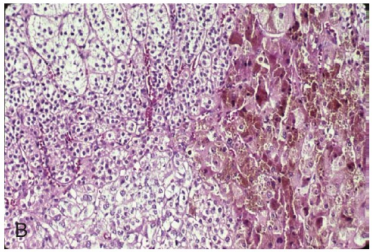
HYPERCORTISOLISM

- Micronodular bilateral adrenal hyperplasia
- ACTH-independent
- Small nodules (<1 cm)
- Two variants: primary pigmented nodular adrenocortical disease or Carney complex (multisystemic disease of endocrine and non-endocrine neoplasms)
- Both variants harbor mutation in cAMP-dependent protein kinase (PRKAR1A gene), producing excessive cAMP

MORPHOLOGY

- Pituitary gland shows Crooke hyaline change (homogenous pale color of corticotroph cells instead of normal granular basophilic cytoplasm), seen in all cases of Cushing syndrome
- Adrenal atrophy (fasciculata and reticularis) is seen in exogenous cause of Cushing syndrome
- ACTH-dependent hyperplasia shows bilateral diffuse enlargement of adrenal glands, variable nodularity and yellow color (grossly), zona reticularis is expanded, eosinophilic and is "lipid poor", surrounded by outer vacuolated "lipid-rich" zona fasciculata. Nodules can be seen and contain "lipid-rich" cells
- Macronodular hyperplasia: multiple large nodules (mixed lipid-rich and poor cells), separated by small nodules
- Micronodular hyperplasia: small dark nodules (black or brown), the pigment is lipofuscin

Diffuse hyperplasia of the adrenal gland contrasted with a normal adrenal gland (top). In cross-section, the hyperplastic adrenal cortex is yellow and thickened, and a subtle nodularity is seen in this gland from a patient with ACTH dependent Cushing syndrome.



(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.

MORPHOLOGY

- Adrenal adenoma can be functional (Cushing syndrome) or non-functional (incidental), both have the same appearance
- Adrenocortical adenoma is surrounded by a capsule, weighs <30g, yellow, microscopically is similar to zona fasciculata cells
- Adrenocortical carcinoma is large (commonly >200 g), not capsulated, anaplastic cells
- Both diseases are more common in women, middle age, show contralateral adrenal atrophy (when functioning)

CLINICAL SYMPTOMS OF CUSHING DISEASE

- Hypertension
- Central obesity, moon face, buffalo hump
- Proximal muscle weakness (atrophy)
- Hyperglycemia, glucoseurea, polyurea, polydipsia
- Bone resorption (osteoporosis)
- Collagen degradation (thin skin, easy bruise, poor wound healing, striation
- Hisrutism
- Menstrual abnormalities
- Immune suppression
- Mental and psychotic disturbances