Adrenal Cortical Carcinomas with Myxoid Differentiation in Ferrets

Signalment

- 5-year-old female ferret
- removed adrenal tumor
  (02/01 bilateral hair loss)
- development of secondary tumor
- widespread metastasis
- necropsy on 11/27/01
- clinical history: wasting away
Gross Lesions

- slightly dehydrated, very thin (500 g)
- abdomen:  - 10 ml clotted blood
  - multiple large masses
- right adrenal gland (5 cm in diameter):
  - homogeneous, soft, pink, central cavitation
  - invaded into abdominal artery
  - rotated 360 degrees clockwise
  - rupture of adrenal artery
  - exsanguination into the abdominal cavity
- necrohemorrhagic mass: severe fat necrosis
- large white, firm, nodular mass in the liver
Morphological Diagnosis

Adrenal Cortical Carcinomas with Myxoid Differentiation
Histochemistry

- myxoid component:
  - negative with Churukian-Schenck argentaffin stain (neuroendocrine cells)
  - mucinous matrix: positive with Alcin blue pH 2.5
Alcian Blue
Immunohistochemistry

- myxoid component:
  - positive: vimentin, a-inhibin
  - variably positive: synaptophysin
  - negative: pancytokeratin, CgA, AFP, SMA
  - increased PCNA LI

- spindle cell component:
  - positive: SMA
Retrospective Study

- 15 ferrets (2 without history)
- age: 5.38 +/- 1.5 years (3-9 years)
- 6 male castrated, 7 spayed female
- neutered > 6 months of age
- clinical signs:
  - hyperestrogenism/space occupying mass
  - polyuria/polydypsia (3/13)
  - symmetric alopecia (13/13)
  - enlarged vulva (3/7), mammary gland (1/7)
  - abdominal distention (4/13)
  - stranguria (3/6), tenesmus (1/13)
Adrenal Tumors

- 0.75 - 5.50 cm in diameter
- no predilection for right or left adrenal
- bilateral tumors (2/13)
- hepatic metastasis (4/13): 1.0-5.0 cm
- metastasis to lung, lymph nodes (1/13)
- myxoid differentiation more prominent in metastatic cases
- metastatic masses were myxoid
Conclusions

• origin of myxoid cells:
  • unknown
  • most likely adrenal cortex, zona reticularis
  • differentiation into mucin producing cells
  • degeneration of neoplastic cells, stroma?
  • ectopic rests of gonadal stromal granulosa or Sertoli cells?! -negative AFP

• effects:
  • feminization, hyperestrogenism
  • more malignant than simple ACC
  • similar variant in humans
Effect of GDX on HPA axis

Non-gonadectomized

Gonadectomized

Hypothalamus

CRH

GnRH

Pituitary

ACTH

LH

Inhibin

Sex steroids

Glucocorticoids

Adrenal

Gonads

Adrenal

Tumor

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Transcription factors implicated in gonadal steroidogenesis

- Hormone
- Receptor
- ATP
- cAMP
- PKA
- Cytoplasm
- Nucleus
- GATA-4
- FOG-2
- Sp1
- SF-1
- C/EBPβ
- DAX-1
- P450c17
- StAR

Transcription factors involved in the regulation of gonadal steroidogenesis, including P450c17, GATA-4, and FOG-2.
Cyt b5 enhances the 17,20-lyase activity of P450c17 through allosteric effects.
Conclusions

- Adrenal glands of healthy ferrets produce only limited amounts of androgenic steroids.
- Adrenocortical neoplasms that arise in neutered ferrets typically secrete androgens or their derivative, estrogen.
- The 17,20-lyase activity of cytochrome P450 17α-hydroxylase/17,20-lyase (P450c17) must increase to permit androgen biosynthesis in neoplastic adrenal tissue.
- Cytochrome-b5 (cyt-b5), an allosteric regulator that selectively enhances the 17,20-lyase activity of P450c17, is a novel marker of gonadal-like differentiation in ferret adrenocortical neoplasms.
- Other sex steroidogenic markers, such as luteinizing hormone receptor, aromatase, and GATA4, are co-expressed with cyt-b5.


