Diagnostic Exercise
From The Davis-Thompson Foundation*
Case **267**; Month: **August**; Year: **2025**

Answer Sheet

Title: Adrenal cortical carcinoma with myxoid differentiation in a ferret.

Contributors: Carolina Fontana[1], Luan Henker[2], Rachel Neto[2]
[1]União Dinâmica de Faculdades Cataratas, Foz do Iguaçu, PR, Brazil
[2]Department of Pathobiology, Auburn University, Auburn, AL, USA
Corresponding author: rtn0004@auburn.edu

History: A 6-year-old, spayed female, 630-g, ferret was evaluated for a 7-day history of progressive lethargy, anorexia, decreased water intake, and abdominal distention. The animal had been previously diagnosed with adrenal disease and was being managed with subcutaneous deslorelin acetate implants. Abdominal ultrasound revealed a large (at least 6.2-cm x 3.6-cm), mixed echogenic mid-abdominal mass. During the ultrasound exam, the patient developed respiratory arrest and died after cardiopulmonary resuscitation was discontinued per owner's decision.

Necropsy findings: The abdomen was severely distended and pendulous. An 8-cm x 6.5-cm x 5-cm, 81-g (12.9% of body weight), encapsulated, multilobulated, dark red to light brown mass was at the caudo-dorsal region, occupying at least 50% of the abdominal cavity, compressing and displacing the left and right kidneys. On the cut surface, the mass was predominantly lobulated, light yellow, and soft, interspersed with a few 5-mm to 2-cm cavitations filled with dark red friable material. The left adrenal gland was not located. A 5-mm x 4-mm x 3-mm cyst was present in the corticomedullary junction of the left kidney, and the spleen was moderately enlarged and meaty. No gross changes were observed in the remaining organs.

Gross and microscopic images:

Figure 1. Ferret, adrenal cortical carcinoma. Body cavities. Abdominal mass occupies at least 50% of the abdominal cavity, compressing and displacing other viscera.
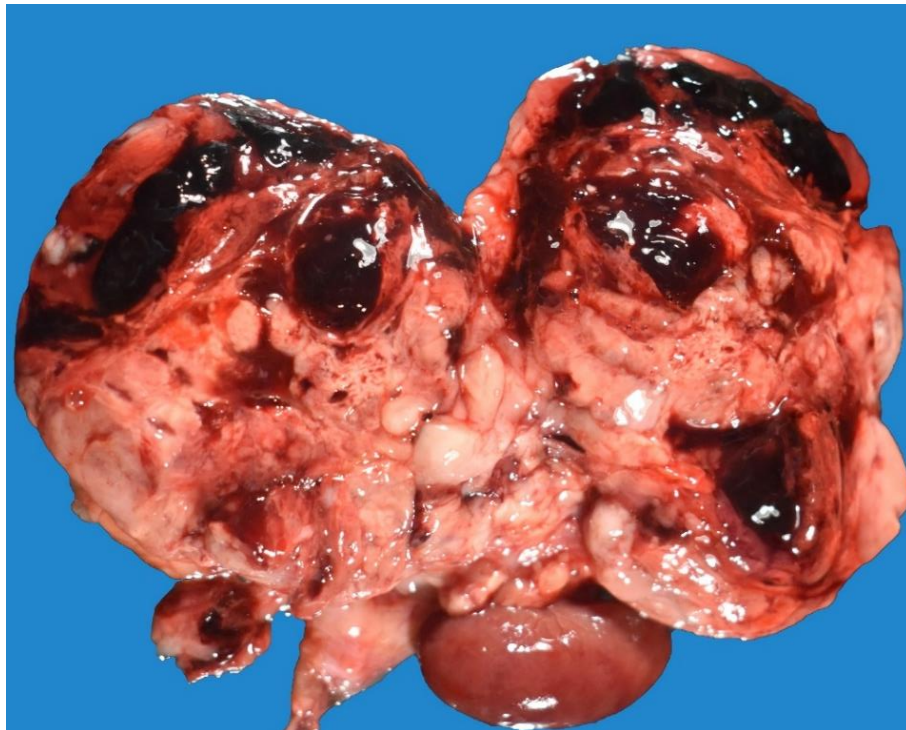
Figure 2. Ferret, adrenal cortical carcinoma. Abdominal mass, cut surface. The mass is lobulated, light yellow, and soft, with cavitations filled with dark red friable material.
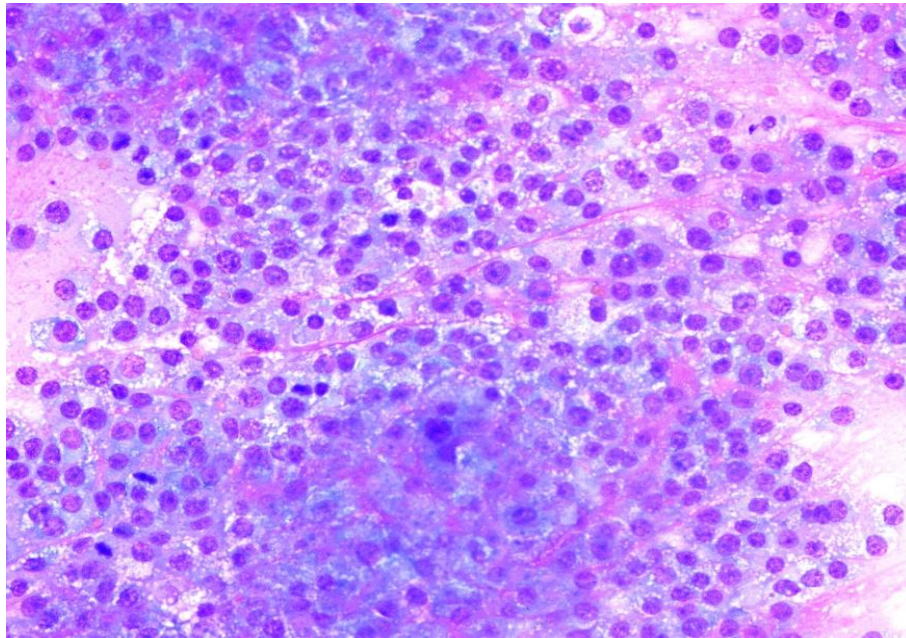

Figure 3. Ferret, adrenal cortical carcinoma. Abdominal mass cytology (impression smear). The sample yielded clusters of polygonal to rounded cells with moderate amounts of finely vacuolated cytoplasm and moderate anisokaryosis. Clusters are surrounded by moderate amounts of extracellular pink material. Romanowsky stain.
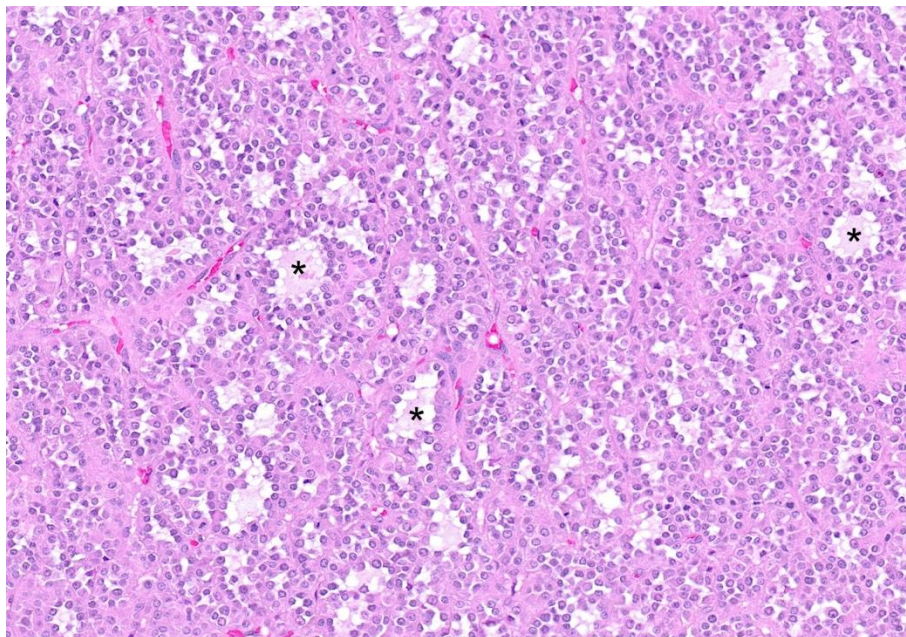

Figure 4. Ferret, adrenal cortical carcinoma. Abdominal mass. The densely cellular neoplasm is composed of polygonal cells arranged in packets, alveoli-like profiles,

and trabeculae, frequently centered on pseudocysts filled with amphophilic material (asterisks). H&E, 10x.
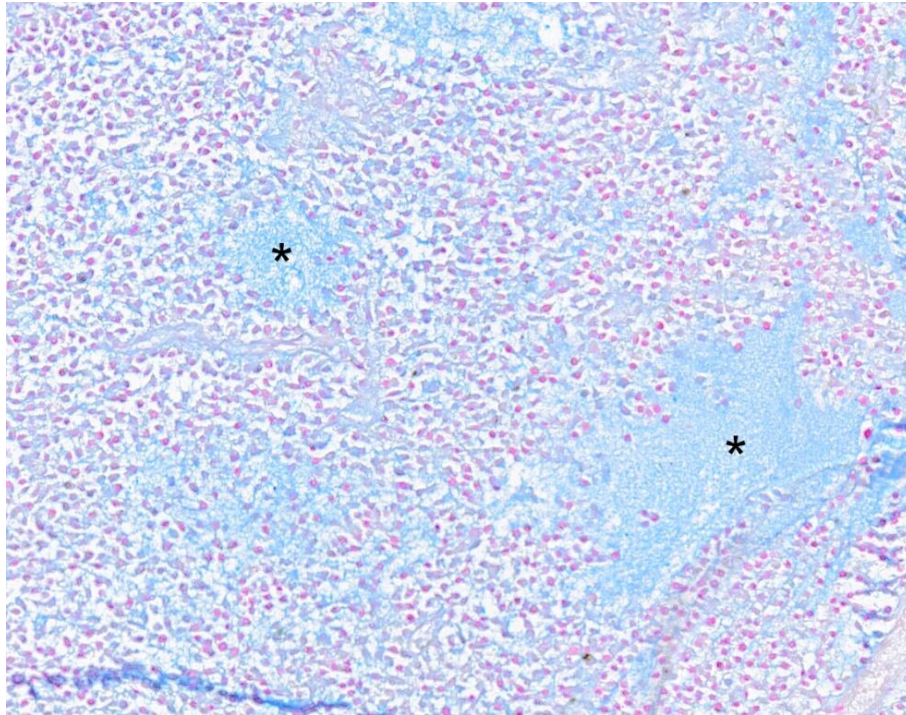

Figure 5. Ferret, adrenal cortical carcinoma. Abdominal mass. Pseudocysts lined by neoplastic cells are filled with moderate amounts of blue wispy material, consistent with mucin (asterisks). Alcian Blue, 10x.
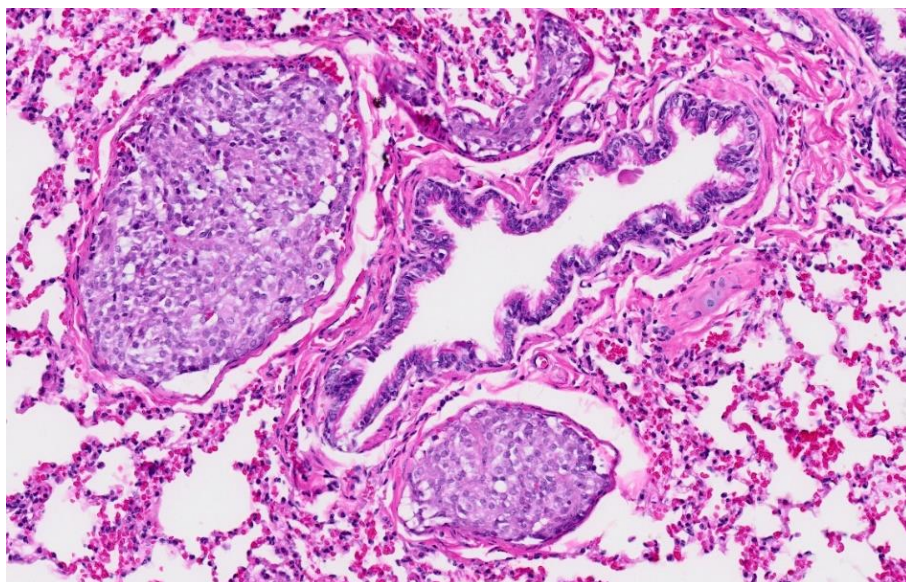
Figure 6. Ferret, adrenal cortical carcinoma. Lung. Blood vessels are partially to completely occluded by aggregates of neoplastic cells. H&E, 10X.

- *Morphologic diagnosi(e)s:*
  1. Intra-abdominal mass (left adrenal gland): Adrenal cortical carcinoma with myxoid differentiation.
  2. Lung: Neoplastic emboli, multifocal.

- *Main clinical and laboratory findings typically associated with this entity:*
  The main clinical signs associated with adrenal disease in ferrets include progressive bilateral symmetrical truncal alopecia, aggressive behavior, pruritus, vulvar enlargement in females, prostatic hyperplasia with squamous metaplasia and secondary urinary obstruction in males, and return to sexually intact behavior in sterilized animals, such as mounting, urine marking, and aggression. In some cases, mammary hyperplasia is observed in castrated males.

  Hormonal evaluations can reveal elevated levels of 17-estradiol and other steroid hormones, such as androstenedione, dehydroepiandrosterone sulfate, and 17-hydroxyprogesterone. Nonregenerative anemia and pancytopenia can be observed as a consequence of estrogen-induced bone marrow toxicity.

- *Main differential diagnoses:*
  The main differential diagnoses for intraabdominal nodules/masses in ferrets are lymphomas, lymphadenitis, insulinomas, and adrenocortical adenomas or nodular hyperplasia.

Comments:

Hyperadrenocorticism secondary to nodular hyperplasia or neoplasia is extremely common in ferrets. Adrenocortical tumors are the second most important neoplastic disease in domestic ferrets, following only insulinomas in prevalence (8). Unlike adrenocortical disease in dogs and cats, where the adrenal glands produce excessive amounts of glucocorticoids, ferret adrenocortical disease is characterized by an increase in the production of androgens, leading to hyperandrogenism (6).

Hyperandrogenism may lead to a plethora of manifestations in ferrets, and the most clinically significant are endocrine alopecia, bone marrow suppression, reproductive, and behavioral changes (6). In this case, the animal had been previously diagnosed with adrenocortical disease and was being managed for an unknown period with subcutaneous deslorelin acetate implants, a depot GnRH-agonist used in the treatment of hyperadrenocorticism in ferrets. The last implant had been placed seven months prior to presentation, and no skin lesions were observed on the clinical examination.

In the United States, most ferrets are neutered before 6 weeks of age. Historically, early neutering (< 6 months of age) has been postulated to be associated with increased risk for adrenocortical disease in ferrets. However, high frequency of adrenocortical disease has also been reported in countries such as the Netherlands, where ferrets are commonly neutered/spayed at ages 8-11 months, immediately before the breeding season. Thus, some authors consider that early surgery is unlikely to be the cause of the high incidence of the disease (6).

A hypothesis proposes that neutering leads to an absence of negative feedback for the hypothalamus in neutered animals. Consequently, under the continuous stimulation of luteinizing hormone, pluripotential cells of the zona reticularis differentiate into cells capable of producing estrogen and other intermediate sex steroid metabolites, including androstenedione and hydroxyprogesterone (4, 6, 8).

Indoor housing has also been suggested as a potential risk factor for the development of adrenal tumors in this species. The daily exposure to artificial light in indoor settings is likely longer than in outdoor settings. As gonadotropins are secreted when the light period exceeds 12 hours per day, indoor ferrets may experience increased plasma concentrations of these hormones for extended periods. This prolonged exposure potentially puts them at a higher risk of developing hyperadrenocorticism compared to ferrets housed outdoors (6).

Adrenocortical proliferative changes observed in ferrets include nodular cortical hyperplasia, adenomas, and carcinomas. These lesions may be unilateral or bilateral. Adrenocortical carcinoma with myxoid differentiation is a rare variant identified in ferrets, cats, and cattle characterized by extracellular accumulations of mucin-like material within the neoplasm (1, 2, 8). A previous case series of adrenocortical carcinomas with mucinous differentiation in ferrets reported robust cytoplasmic immunolabeling within areas of themyxoid component when using the anti-vimentin and anti–α-inhibin antibodies, and these cells exhibited a faint and variable cytoplasmic labeling for anti-synaptophysin (4). Immunohistochemistry stains were noncontributory in our case.

The mucinous matrix within lumen-like structures in regions exhibiting myxoid differentiation in all adrenocortical carcinomas showed positive staining with alcian blue (4,3). Metastatic lesions are rarely described with adrenal adenocarcinomas in ferrets, but, when found, they are most commonly seen in the liver, regional lymph nodes, and less frequently in the lung. In this case, a large number of pulmonary vessels contained neoplastic emboli.

The differential diagnosis to intraabdominal nodules/masses in ferrets include lymphomas, lymphadenitis, and insulinomas. Among them, insulinoma stands out as the most common neoplasm in these animals, with a prevalence of 20 to 25% of the diagnosed neoplasms in ferrets. These endocrine tumors do not show a sexual predilection and mainly affect middle-aged animals (2-8 years). Unlike what is observed in dogs, insulinomas in ferrets have a low metastatic potential (6, 8). The main clinical signs include lethargy, ataxia, incoordination, seizures, and loss of

consciousness, secondary to hypoglycemia caused by the production of insulin by the tumor tissue (6).

Lymphomas can also present as abdominal masses in ferrets, mainly located in mesenteric lymph nodes, spleen, liver, and bone marrow. Lymphomas are the third most prevalent neoplasm in young and neutered ferrets, often reported in association with insulinomas and adenocarcinomas (7). Clinical signs are nonspecific and may include decreased appetite, lethargy, lymphadenomegaly, peritoneal, and hepatic effusion, and hepatosplenomegaly. Although genetic alterations are described as predisposing factors for lymphoma development in humans and other animal species, this association is not described in ferrets, nor is their development associated with infectious diseases (8). Abdominal ultrasound examination shows mesenteric lymphadenomegaly; however, this change can also be seen with chronic *Helicobacter mustelae* infections, which is an important differential diagnosis for the disease (7).

Finally, enlarged visceral lymph nodes manifesting as palpable abdominal masses can be a feature of ferret systemic coronavirus-associated disease, which closely resembles feline infectious peritonitis. Granulomatous-to-pyogranulomatous inflammation is the histologic hallmark of the disease, usually affecting lymph nodes, spleen, kidneys, and serosal surfaces. In addition, a low albumin-to-globulin ratio is a typical biochemistry finding of this viral disease (5).

References:

1. Attipa C, Lipscomb V, English K, Carvalho S, Kiupel M, Szladovits B, Peters LM. Aldosterone-producing adrenocortical carcinoma with myxoid differentiation in a cat. Vet Clin Pathol. 2018;47:660–4.

2. Grossi AB, Leifsson PS, Jensen HE, Vainer B, Iburg T. Histologic and immunohistochemical classification of 41 bovine adrenal gland neoplasms. Vet Pathol. 2013;50:534–42.

3. Householder HM, Cassmann ED, White R, Fales-Williams A, Viall AK, Zaffarano BA. Paraplegia in a domestic ferret (*Mustela putorius furo*) secondary to metastatic adrenocortical carcinoma with myxoid differentiation. J Exot Pet Med. 2019;29:63–9.

4. Peterson RA, Kiupel M, Capen CC. Adrenal cortical carcinomas with myxoid differentiation in the domestic ferret (*Mustela putorius furo*). Vet Pathol. 2003;40(2):136–42.

5. Puffal J, Neece AJ, Scaletti F. Treatment of three ferrets diagnosed with ferret systemic coronaviral disease using the nucleoside analogue GS-441524. Animals (Basel) 2024;14(6):916.

6. Rosenthal KL, Wyre NR: Endocrine disease, In: Ferrets, Rabbits, and Rodents: Clinical, Medicine and Surgery. 4th ed. Missouri: Elsevier; 2020. p 77–91.

7. Schoemaker NJ. Ferret oncology: diseases, diagnostics, and therapeutics. Vet Clin North Am Exot Anim Pract. 2017;20(1):183–208.

8. Williams BH & Wyre NR. Neoplasia in ferrets. In: Ferrets, Rabbits, and Rodents, editors. Clinical, Medicine and Surgery. 4th ed. Missouri: Elsevier; 2020. p.92–108.

*The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation (DTF). These exercises are contributed by members and non-members from any country of residence. Consider submitting an exercise! A final document containing this material with answers and a brief discussion will be posted on the DTF website.

(https://davisthompsonfoundation.org/diagnostic-exercise/)

Associate Editor for this Diagnostic Exercise: Saulo Pavarini
Editor-in-chief: Claudio Barros