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METASTATIC, PAPILLARY CYSTADENOCARCINOMA OF THE MAMMARY GLAND IN A BLACK-FOOTED FERRET

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Abstract: A simple, papillary cystic adenocarcinoma of the mammary gland with metastases to the internal iliac and mesenteric lymph nodes, liver, and spleen was observed in a 12 to 13 year old female black-footed ferret (*Mustela nigripes*). Histologically, the tumor was aggressive, and lymphatic invasion was found. Attempts at virus isolation were negative. Other findings were bilateral infarcts in the kidneys, apparently resulting in acute renal shutdown and death, multiple thrombi in the right atrium, aortic arteriosclerosis, and focal interstitial pneumonia.

INTRODUCTION

The black-footed ferret (*Mustela nigripes*) is probably the rarest and most endangered mammal in North America. There have been only a few sightings since 1973, and none of these individuals were ever observed again. As an adjunct to field studies, habitat preservation, and legal protection, 5 ferrets live-trapped in South Dakota in 1971-73 were transported to the Patuxent Wildlife Research Center to establish a captive population for study and production of suitable stock for restoring or bolstering populations in the wild.⁵

CASE HISTORY

On 18 June 1978, a mass was observed on the dorsal surface of the tail of a 12 to 13 year old female ferret, maintained at the Patuxent Center since 1973. The firm growth, surrounded by reddish-white skin, measured 1 × 1 × 1 cm, and was located 3 cm from the base of the tail. No

evidence of metastasis was detected on radiographic examination. The ferret was anesthetized, and the mass together with the surrounding adventitia were excised. The mass was tan-white and fat-like on cross section. The surrounding dermis was brownish. Based on a histologic diagnosis of a basal cell carcinoma,³ a caudectomy was performed on June 19.

The ferret was again hospitalized on 21 December 1978, for anorexia, dehydration and weight loss. A large, firm mass was palpated under the skin of the right thigh, extending into the inguinal area. Microscopic examination of a needle aspirate from the mass revealed amorphous debris. In addition to the mass, moderate cardiomegaly and arteriosclerosis of the thoracic aorta were evident on radiographs.

The ferret's condition declined despite intensive care, including intermittent force-feeding. On 31 December, the animal was weak, anorexic, ataxic and died 3 days later.

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NECROPSY FINDINGS

The ferret was very thin, weighing 944 g. Subcutaneous edema was present on the ventral cervical, thoracic and abdominal areas. A large, firm mass (28 mm × 20 mm) was located under the skin of the right thigh and inguinal area. The mass was off-yellow with orange mottling. An additional yellow-white mass (8 mm × 6 mm) was located ventral to the large mass. Similar appearing masses were found in the liver, spleen, an internal iliac lymph node and the mesentery.

Small amounts of clear, orange-tinged transudate were present in the thoracic and abdominal cavities. The lungs were congested with multifocal, irregular tan areas on the surface. These measured 2-3 mm and several felt gritty. The heart was moderately distended with several pale streaks in the myocardium. The aorta, from the base of the heart to the anterior abdominal cavity, contained a series of firm, roughened rings of pale yellow mineral deposits. The kidneys were pale-tan with several large greenish-tan to purple lesions in the cortex and medulla. An area of cicatrix was present on the surface of one kidney.

HISTOLOGIC FINDINGS

Tissue specimens were fixed in buffered-neutral 10% formalin, embedded in paraffin, sectioned at 6 μ m, and stained with hematoxylin and eosin (H & E). The primary inguinal mass was a mammary tumor (Fig. 1) composed of large, aggregations or cords of neoplastic cells with extensive necrotic central cores and surrounded by fibrous connective tissue (Fig. 2). In some areas, the peripheral border of the neoplasm was characterized by papillary projections. The tumor was aggressive, and had invaded lymphatics. The nuclei of the neoplastic tumor cells were round to ovoid, commonly pleomorphic, had enlarged nucleoli, and on occasion were hyperchromatic. The mitotic index was low.

Additional foci of similar neoplastic tissue were identified in the liver and spleen and in the internal iliac and mesenteric lymph nodes. In the liver, the tumor tissue had elicited a severe fibrotic

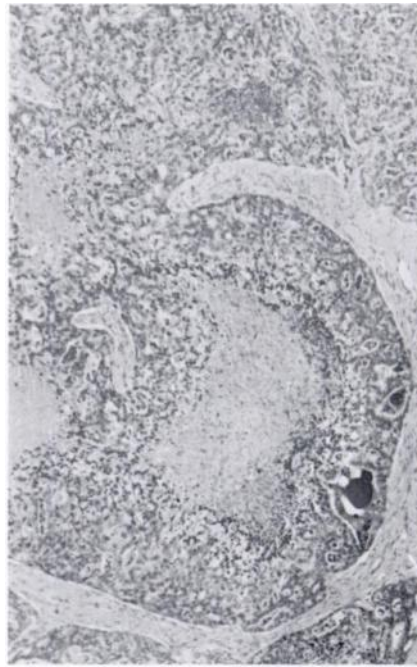


FIGURE 1. Primary mammary neoplasm excised from the subcutis of the ventral abdominal region of a black-footed ferret. H&E × 24

reaction and was highly anaplastic (Fig. 3) with considerably fewer glandular acini than in other sites.

Other significant histopathologic findings included multiple mural thrombi in the right atrium, extensive renal infarction, medial calcification in the ascending and thoracic aorta, bilateral adrenal nodular hyperplasia, extramedullary hematopoiesis in the liver, atrophy of skeletal muscles, and moderate to severe focal suppurative interstitial pneumonia.

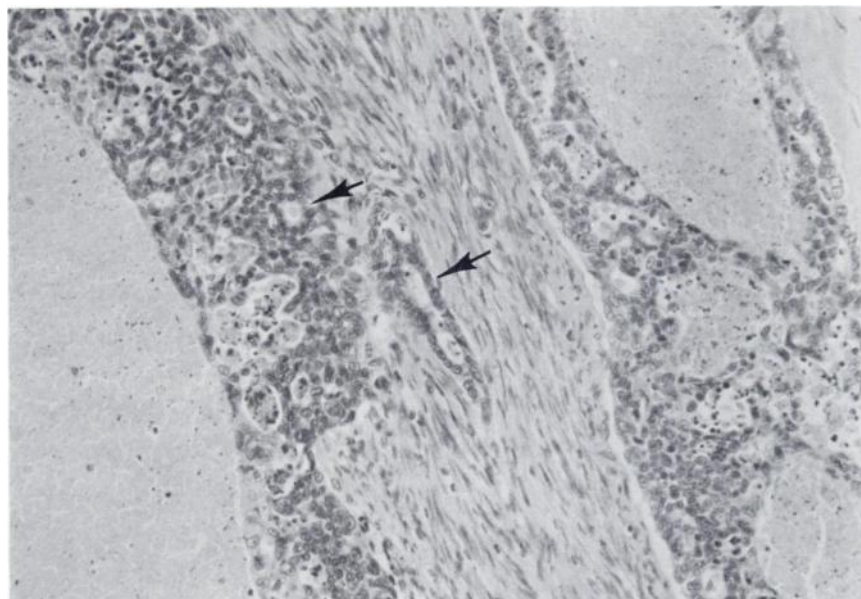


FIGURE 2. Higher magnification of neoplastic tissue characterized by acinar and ductular profiles (arrows), stromal fibrosis, and extensive necrosis. H&E \times 96

DISCUSSION

The methods of classifying mammary tumors vary considerably because of the many criteria that have been proposed.⁸ We have, therefore, classified the tumor in the black-footed ferret as a simple, papillary cystic adenocarcinoma, based primarily on the morphologic arrangement of the neoplastic cell type as outlined by The World Health Organization (1974).⁶ The term "simple" implies that only one cell type, the epithelial cell, is involved in the neoplastic process.

Mammary tumors have been reported in many species of domestic⁸ and laboratory animals¹² but, apparently, rarely are observed in wild or exotic animals. Mammary tumors rank behind skin tumors as the most common neoplasm in the canine;⁸ and represent 25 to 30% of all tumors of the bitch.¹ Aside

from skin and the lymphoid and hematopoietic tissues, the most common site for neoplasia in the cat is the mammary gland.⁸ The percentage of mammary tumors that are carcinomatous is much higher in the cat than in the dog.⁹ Reports of neoplasms in the ferret are rare, and mammary gland tumors have not been reported.¹⁰ The ferret tumor is similar, histologically, to that described for the dog.⁶

The cause of mammary tumors in laboratory animals and man is believed to involve complex events, some of which are: radiation, chemicals, viruses, hormones, immune status, genetics, age and nutrition. The interaction of two or more of these factors ultimately leads to the genesis of mammary neoplasia.¹¹ The cause of the tumor in this ferret is undetermined. Attempts at viral isolation ¹³

¹³ In cell monolayers, 1 to 3 days old, prepared from kidney and spleen of a young European ferret (*M. putorius*) at passage levels two through four.

from both the primary and metastatic tumor masses were negative. The tumor may be a reflection of the old age of this animal. There is a higher risk of mammary cancer in old than in young dogs, although the age-specific rate of incidence decreases in the bitch after 10-11 years of age.⁸ Feline mammary growths tend to arise at an older age, with the average of 11.5 years reported in one survey.⁴

The cystadenocarcinoma in the ferret metastasized widely, retaining its ability to form ducts and acini with attempts at both papillary and cystic formation. Metastases occur in about 25% of canine mammary carcinomas⁸ and in 32% of feline mammary neoplasms.⁴ Invasion of lymphatics, as seen in this ferret, is rare in most species, although it

sometimes occurs in feline papillary cystadenocarcinomas.⁸

Multiple thrombi were observed in the right atrium and may have been a factor in the protracted malaise of the patient. Extensive infarcts were present in both kidneys and apparently resulted in renal insufficiency, leading to the death of the ferret. Origin of the renal thrombi is unknown, although atrioventricular shunts through the lung may have permitted emboli to pass from the right atrium into the systemic circulation. The medial calcification of the ascending and thoracic aorta in this patient has been reported to occur more commonly in animals of advancing age, and is frequently associated with a variety of debilitating diseases such as chronic renal insufficiency and uremia.⁷ Foci of

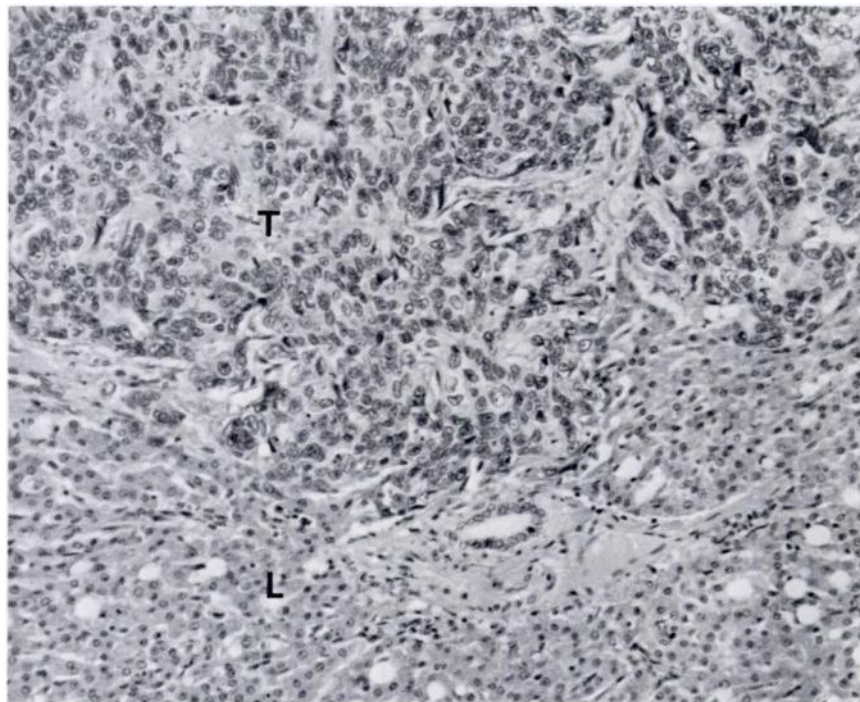


FIGURE 3. Metastatic tumor in the liver (L), composed of highly anaplastic cells (T). H&E $\times 96$

interstitial pneumonia and extramedullary hematopoiesis in the liver are apparent sequellae of the cachexic condition of the ferret. The adnexal gland tumor removed from the tail 6 months before the ferret's death was not related to the pathologic findings at postmortem examination.

Between 1976 and 1978, all five black-footed ferrets maintained at Patuxent developed adnexal tumors, classified as adenocarcinomas (both sweat and sebaceous gland origin) or basal cell carcinomas.³ The etiology and significance of the mammary gland cystadenocarcinoma in this ferret and

the other tumors and pathologic disorders previously reported in this five-member colony are not known with certainty.^{2,3} The pathology observed in the captive black-footed ferrets has not been observed in any of the 250 or more European and Siberian ferrets (*M. eversmanni*) also maintained at the Patuxent Center. The tumors and concurrent pathology in the black-footed ferret may be a reflection of pathological processes occurring in the wild population, and these processes may actually be partly responsible for the recent decrease in the number of wild ferrets. No black-footed ferrets are currently known to exist in captivity.

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