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PARAPLEGIA IN A DOMESTIC FERRET (MUSTELA PUTORIUS FURO) SECONDARY TO METASTATIC ADRENOCORTICAL CARCINOMA WITH MYXOID DIFFERENTIATION

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Abstract

Neurologic disease is a common presentation of domestic ferrets (Mustela putorius furo) with infectious, neoplastic, and traumatic etiologies documented. Adrenocortical neoplasia is also well documented in domestic ferrets, with metastatic lesions rarely described. This case report describes an abnormal presentation of adrenocortical adenocarcinoma with myxoid differentiation and subsequent metastasis to the spinal cord and vertebral bodies, resulting in hind limb paraplegia in an adult spayed female ferret. Copyright 2018 Elsevier Inc. All rights reserved.

Key words: Ferret; adrenocortical adenocarcinoma; myxoid; metastasis; paraplegia

CASE PRESENTATION

A 4-year-old female spayed ferret (Mustela putorius furo) presented to the Iowa State University College of Veterinary Medicine Lloyd Veterinary Medical Center for a 2-day history of progressive hindlimb paraparesis, lethargy, loss of bladder control, and tail paralysis. The ferret had a history of a cutaneous mast cell tumor over the right antebrachium and low-grade second degree atrioventricular block.

She presented to her primary care veterinarian 4 days prior for difficulty ambulating and was assessed as having a wobbly pelvic limb gait, abnormal proprioception of the pelvic limbs, and a cardiac arrhythmia. Blood glucose was mildly decreased at 76 mg/dL (reference interval 80 to 117 mg/dL). Whole body radiographs revealed suspected cardiomegaly and no obvious spinal pathology. On presentation to the Lloyd Veterinary Medical Center, the ferret was assessed with absent motor function in the right pelvic limb and minimal motor function in the left pelvic limb with nociception intact bilaterally. A neurologic exam localized the lesion to the spinal cord between the third thoracic vertebrae and the third lumbar vertebrae (T3 to L3) based on conscious proprioception deficits in the pelvic limbs, a small amount of motor function in the left hind limb, lack of motor function on the right hind, and normal anal tone. Reaction to noxious stimuli was present in both hind limbs. The previously diagnosed mast cell tumor and cardiac arrhythmia were unchanged. The remainder of the physical exam was unremarkable. A complete blood count revealed mild elevation in hematocrit (54.9%; reference interval 36% to 48%) and hemoglobin (18.4 gm/dL; reference interval 12.2 to 16.5 gm/dL) and a serum biochemistry panel revealed mild elevation in albumin (4.2 gm/dL; reference interval 2.5 to 4.0 gm/dL) and BUN (45 mg/dL; reference interval 18 to 32 mg/dL)
which were attributed to dehydration. Magnetic resonance imaging (MRI) of the thoracolumbar spine was performed using a 1.5-T system (GE Signa Horizon 1.5 T). The patient was positioned in dorsal recumbency. T2-weighted (T2W) fast recovery fast spin echo sequence were obtained in the sagittal plane, a T2W fast recovery fast spin echo sequence was obtained in a transverse plane, and a soft tissue inversion recovery sequence was obtained in a dorsal plane. All sequences were obtained without intravenous contrast administration due to length of procedure, hypothermia, and anesthesia concerns. On the T2W transverse sequence, a left sided hyperintensity was noted in the spinal canal spanning from the cranial aspect of the T12 vertebral body to the caudal aspect of the T13 vertebral body (Fig. 1A). This hyperintensity caused moderate rightward compression of the spinal cord. On the sagittal sequence, complete loss of cerebrospinal fluid signal was evident (Fig. 1B). On the T2W transverse sequence was a well-marginated bilobed mass ventral to L2, just left of midline and cranial to the left kidney, consistent with a left adrenal mass. The presumptive adrenal mass measured 1.3 by 0.9 cm and was mildly hyperintense to the splenic parenchyma (Fig. 2). The T2 hyperintensity located within the spinal canal was 2.8 cm cranial to the cranial pole of the left adrenal gland with no communication noted between the lesions. The primary differentials for the spinal canal lesion included neoplasia (such as, lymphoma, a peripheral nerve sheath tumor, or metastasis of the previously diagnosed mast cell tumor), hemorrhage or hematomata, or fat. Neoplasia was considered the highest differential based on the clinical signs, lack of traumatic history, and loss of cerebrospinal fluid signal. Exploratory surgery was offered and declined with palliative therapy chosen. The ferret was started on prednisolone 1 mg/kg orally, once a day (Qualitest Pharmaceuticals, Huntsville, AL USA) and famotidine 0.5 mg/kg orally, once a day (Iowa State University, Ames, IA USA).

She presented for a recheck 1 month later. The owner reported that the ferret was completely urinary and fecal incontinent and had mildly decreased energy. Physical examination revealed hind limb paraplegia with deep pain nociception intact and decreased muscle mass of the pelvic limbs. Her bladder was easily expressed. The remainder of her physical exam was unremarkable. Based on the high prevalence of lymphoma in domestic ferrets and the presence of adrenal disease with possible subsequent metastasis to the liver, fine needle aspirates were taken of the liver and spleen in an attempt to obtain a diagnosis without pursuing a spinal biopsy. The fine needle aspirates were consistent with blood and extramedullary hematopoiesis, respectively. The current treatment plan was continued with suggestions for a custom-fit wheelchair, regular bladder expression and consideration for spinal biopsy.

The ferret presented 7 months later out of owner concerns that the spinal mass was growing and a thinning haircoat. On presentation, the ferret had hind limb paraplegia with significant muscle atrophy, a firm fixed mass slightly left of midline measuring 4 × 2.5 cm over her thoracic spine, an irregular nodular left abdominal mass, and bilateral truncal alopecia. Abdominal ultrasound revealed a large left-sided cavitated abdominal mass. Fine needle aspirates of the abdominal and spinal masses were taken (Fig. 3). Cytology revealed atypical epithelial cells, many of which were enveloped within streaming, amphiphilic material. The atypical epithelial cells ranged from round to polygonal to oval in shape. Moderate anisocytosis was evident and the cells had a moderate N:C ratio and contained round, variably positioned nuclei with open chromatin and 0 to 2 nucleoli. Occasional binucleated and multinucleated variants were found. The owner elected to continue palliative care.

Two weeks later the ferret was euthanized and the body was submitted for postmortem examination. Gross examination of the external body revealed bilateral symmetrical truncal hypotrichosis. The peritoneal cavity contained an expansile 5 × 7 cm multilobular mass (Fig. 4) that attached to the dorsal body wall at the caudal thoracic vertebral column. Both of the kidneys were intimately associated with the mass, however, the mass did not penetrate the renal capsules. The abdominal mass was highly vascularized, and on the cut surface, the mass exuded a sticky viscous substance. Other gross findings included small 1 to 2 mm tan nodules on the pulmonary pleura and multifocal mucosal reddening of the small intestine.

Microscopically, the mass was void of discernable native architecture. Cells were arranged in chords, sheets, and smaller nests along a fine fibrovascular stroma with broad interlobular bands of fibrous connective tissue (Fig. 5). The cytoplasm appeared eosinophilic to amphophilic. The nucleus of cells was round with granular clumped chromatin, frequently containing a single nucleolus. The mitotic count was 9 per 2.37 mm². Multifocally cells contained variably-sized indistinct vacuoles. Pockets of cells were
multifocally separated by islands of granular to fibrillar basophilic substance that coalesced to larger homogenous pools. Multiple regions of necrosis and hemorrhage appeared within the mass. Focally the abdominal mass invaded the caudal thoracic vertebral column (Fig. 6). This was characterized microscopically by partial effacement of the annulus fibrosus, nucleus pulposus, and the adjacent vertebral body. The neoplasm also invaded and effaced the spinal cord at this location (Fig. 6). Histochemical and immunohistochemical methods further characterized the abdominal neoplasm. Islands of matrix within the abdominal mass were positive for either periodic acid-Schiff or alcian blue pH 2.5 (Fig. 7A and B). The preponderance of neoplastic cells expressed mild to strong cytoplasmic reactivity for Melan-A (Fig. 8). Concurrently, neoplastic cells were negative for synaptophysin and chromogranin-A. A few scattered cells adjacent to islands of matrix were cytokeratin positive, but as a whole, the neoplasm lacked immunoreactivity for this marker. The morphologic and immunohistochemical findings were consistent with an adrenocortical carcinoma with myxoid differentiation.

Other microscopic lesions included multifocal endogenous lipid pneumonia (lipid granulomas corresponding with the 1 to 2 mm tan masses observed grossly), pulmonary microthrombosis, pulmonary arteriolar mineralization, myocardial mineralization, focal islet cell tumor (insulin negative), lymphoplasmacytic interstitial nephritis,
lymphoplasmacytic eosinophilic enteritis, and hepatic lipidosis.

DISCUSSION

Neurologic diseases are common in pet ferrets (*Mustela putorius furo*), with the most common presenting complaint of paraparesis and ataxia. Clinical presentations of neurologic disease in ferrets is most commonly related to systemic illness rather than primary neurologic disease. Many infectious agents can cause neurologic signs in ferrets such as bacterial diseases, including...
Clostridium botulinum, viral diseases such as canine distemper virus, Aleutian disease, ferret systemic coronavirus, and rabies, or fungal diseases, such as Cryptococcus species or systemic blastomycosis. Neoplastic causes of neurologic signs in ferrets include lymphoma, insulinomas, chordomas or chondrosarcomas, osteomas, fibrosarcomas, and plasma cell myelomas. Other causes of neurologic disease in ferrets include primary spinal cord disease such as intervertebral disc disease, spinal malformations, trauma to the vertebrae or spinal cord, and toxicities.

Adrenocortical disease is a common problem in domestic ferrets and is most commonly seen in middle-aged to older ferrets. In contrast to adrenocortical disease in dogs and cats where the adrenal gland overproduces glucocorticoids, ferret adrenal disease is characterized by the overproduction of androgens. The underlying cause of adrenal disease in ferrets is unknown, but suggested causes include early neutering, genetic predisposition, and husbandry related issues such as disruption in the light-dark cycle or diet. Common clinical signs of adrenal disease in ferrets include progressive bilaterally symmetrical truncal alopecia, pruritus, aggression, vulvar enlargement in female ferrets, and prostatomegaly with subsequent urinary obstruction in males. Differential diagnoses include ovarian remnant syndrome and seasonal alopecia. Diagnostic tests used to evaluate adrenal disease in ferrets include ultrasonographic evaluation of the adrenal glands and analysis of androgen levels in the blood including estradiol, androstenedione, and 17α-hydroxyprogesterone; complete blood counts are recommended to assess for nonregenerative anemia secondary to estrogen-induced pancytopenia and chemistry panels are used to screen for other common diseases such as insulinomas.

Two common treatment options for adrenal disease include surgical excision of the affected adrenal gland and medical management. A unilateral adrenalectomy is recommended if only...
one adrenal gland is affected; if both glands are affected, subtotal adrenalectomies are preferred as bilateral total adrenalectomies typically resulted in the need for postprocedure glucocorticoid and mineralocorticoid supplementation.9,12 Survival rates are not significantly different between partial and complete resections, however, partial resection followed by cryosurgery are associated with shorter survival times.12 Medical management of adrenal disease is achieved in ferrets via the use of the gonadotropin-releasing hormone agonists which provide down-regulation of pituitary GnRH receptors, thus limiting the production of androgens.9,11 Ferrets that undergo medical management with a 4.7 mg deslorelin implant are shown to have a longer time from treatment to return of clinical signs than those treated surgically.13 On histopathologic examination, adrenal disease is characterized by unilateral or bilateral adrenal gland hyperplasia, adenoma, or carcinoma.3,9,11 Metastasis to other organs is uncommon, but local invasion of the vena cava or liver have been described as well as rare metastasis to the lungs.9 Previously described variants of adrenocortical carcinomas in ferrets include spindle cell variants and carcinomas with myxoid differentiation.9,14,15 Adrenocortical carcinomas with myxoid differentiation have been rarely reported in human literature, but have been associated with malignancy.15,16 This case represents an unusual presentation of adrenal disease in ferrets and is the first report documenting the clinical progression of a ferret with adrenocortical carcinoma with myxoid differentiation. Based on cytology and histopathology, the spinal tumor was most likely a metastatic lesion from the primary adrenal tumor. The cellular origin of the abdominal mass was initially obscured due to its size and the effacement of native histologic architecture. Morphologically, the neoplasm exhibited characteristics typical of an endocrine carcinoma that could have been consistent with adrenal origin. Melan-A has been used as a discriminatory marker for adrenal cortical cells in humans and dogs.17,18 Since this antibody is readily available in our diagnostic laboratory, it was chosen as an adrenal cortical marker; ancillary validation of the antibody in normal ferret adrenal gland indicated interspecies histocompatibility (unpublished data). Subsequently, the neoplasm demonstrated positive immunoreactivity for Melan-A consistent with an adrenal cortical origin. Concurrent negative immunoreactivity for synaptophysin and chromogranin-A further discriminated the neoplasm from adrenal medullary origin. Alcian blue and periodic acid-Schiff reactivity characterized the neoplasm’s associated matrix as a carbohydrate mucosubstance.19 Initially, this ferret did not present with any of the common clinical signs typically associated with adrenal disease. Treatment for the adrenal disease was not initiated when the adrenal mass was found due to absence of clinical disease. The primary differentials for the spinal lesion at the time of discovery were lymphoma, a peripheral nerve sheath tumor, or less likely, a metastatic mast cell tumor, given the history of the right antebrachial mast cell tumor. Metastatic lesions are rarely described with adrenal adenocarcinomas. Based on the MRI findings of 2 distinct lesions, the spinal lesion is suspected to be metastatic spread of the primary adrenal mass rather than local invasion to the spinal cord and associated vertebrae. Due to location within the spinal column at time of the MRI, a surgical biopsy was not pursued. Had treatment been initiated at the time the adrenal mass was identified, it is unlikely the clinical course would have been significantly affected. Surgery in this case would not have been curative as the adrenal mass had already metastasized to the spinal cord and medical management of adrenal disease primarily serves to control the clinical signs of the disease, but does not have a significant impact on limiting the growth of the tumor.

REFERENCES

1. Diaz-Figueroa O, Smith MO: Clinical neurology of Ferrets. Vet Clin Exot Anim 10:759–773, 2007
2. Antinoff N, Giovanella CF: Musculoskeletal and Neurologic Diseases, in Quesenberry KE, Carpenter JW (eds): Ferrets, Rabbits, and Rodents Clinical Medicine and Surgery, (ed 3). St. Louis, MO, Saunders/Elsevier, pp 132–140, 2012
3. Mayer J: Clinical Veterinary Advisor: Birds and Exotic Pets, in Donnelly TM (ed): St. Louis, MO, Saunders/Elsevier, pp 430–482, 2013
4. Murray J, Käupel M, Maes RK: Ferret coronavirus-associated diseases. Vet Clin Exot Anim 13:543–560, 2010
5. Pye GW, Bennet A, Roberts GD, et al: Thoracic vertebral chordoma in a domestic Ferret (Mustela putorius furo). J Zoo Wildl Med 31:107–111, 2000
6. Methiyapun S, Myers RK, Pohlenz JFL: Spontaneous plasma cell myeloma in a Ferret (Mustela putorius furo). Vet Patho 22:517–519, 1985
7. Morera N, Valls X, Mascort J: Intervertebral disk prolapse in a Ferret. Vet Clin Exot Anim 9:667–671, 2006
8. Orlandi R, Mateo I: Intervertebral disc protrusion in a Ferret with triple thoracic block vertebrae. J Exotic Pet Med 22:396–399, 2013
9. Rosenthal KL, Wyre NR: Endocrine Disease, in Quesenberry KE, Carpenter JW (eds): Ferrets, Rabbits, and Rodents Clinical Medicine and Surgery, (ed 3). St. Louis, MO, Saunders/Elsevier, pp 86–102, 2012
10. Shoemaker NJ, Schuurmans M, Moorman H, et al: Correlation between age at neutering and age at onset of
hyperadrenocorticism in ferrets. J Am Vet Med Assoc 216:195–197, 2000

11. Chen S: Advanced diagnostic approaches and current medical management of insulinomas and adrenocortical disease in Ferrets (Mustela putorius furo). Vet Clin Exot Anim 13:439–452, 2010

12. Swiderski JK, Seim HB, MacPhail CM, et al: Long-term outcome of domestic ferrets treated surgically for hyperadrenocorticism: 130 cases (1995-2004). J Am Vet Med Assoc 232:1338–1343, 2008

13. Lennox AM, Wagner R: Comparison of 4.7 mg deslorelin implants and surgery for the treatment of adrenocortical disease in Ferrets. J Ecot Pet Med 21:332–335, 2012

14. Newman SJ, Bergman PJ, Williams B, et al: Characterization of spindle cell component of ferret (Mustela putorius furo) adrenal cortical neoplasms—correlation to clinical parameters and prognosis. Vet Comp Oncol 2:113–124, 2004

15. Peterson RA, Kiupel M, Capen CC: Adrenal cortical carcinomas with myxoid differentiation in the domestic Ferret (Mustela putorius furo). Vet Pathol 40:136–142, 2003

16. Papotti M, Volante M, Duregon E, et al: Adrenocortical tumors with myxoid features: a distinct morphologic and phenotypical variant exhibiting malignant behavior. Am J Surg Pathol 34:973–983, 2010

17. Ramos-Vara JA, Beissenherz ME, Miller MA, et al: Immunoreactivity of A103, an antibody to Melan A, in canine steroid-producing tissues and their tumors. J Vet Diagn Invest 13:328–332, 2001

18. Zhang PJ, Genega EM, Tomaszewski JE, et al: The role of calretinin, inhibin, melan-A, BCL-2, and C-kit in differentiating adrenal cortical and medullary tumors: an immunohistochemical study. Mod Pathol 16:591–597, 2003

19. Kiernan JA: Histological and Histochemical Methods: Theory and Practice. p 1, ed 3 London: this impr. publ. Arnold; 2005. p. 1–502, 2005