Intestinal Lymphoma of Granular Lymphocytes in a Fisher (*Martes pennanti*) and a Eurasian Otter (*Lutra lutra*)

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INTESTINAL LYMPHOMA OF GRANULAR LYMPHOCYTES IN A FISHER (*MARTES PENNANTI*) AND A EURASIAN OTTER (*LUTRA LUTRA*)

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Abstract: Intestinal lymphoma of granular lymphocytes was diagnosed in a 6-year-old fisher (*Martes pennanti*) and a geriatric Eurasian otter (*Lutra lutra*). Clinical signs included lethargy and inappetance in both animals and vomiting and occasional diarrhea in the fisher. The diagnosis in both cases was made using cytology of fresh tissue, histology of fixed tissues, and immunohistochemistry. Granules were seen most clearly on cytologic examination of direct impressions from fresh tissue. Because granules were absent in most histologic sections, cytology of fresh tissue was essential for the diagnosis. Immunohistochemistry determined that the neoplastic cells had positive membranous immunoreactivity to CD3 and were negative for CD79a, which was consistent with alimentary T-cell lymphoma. The disease course in both animals was presumed to be aggressive, with rapid progression of clinical signs, high mitotic index and effacement of local intestinal architecture in both cases, and metastatic disease in the fisher. To the authors' knowledge, this is the first report of lymphoma of granular lymphocytes in a fisher and a Eurasian otter.

Key words: Eurasian otter, fisher, immunohistochemistry, *Lutra lutra*, lymphoma, *Martes pennanti*.

INTRODUCTION

Neoplasia in wild and captive wild *Mustelidae* is uncommonly documented in the literature.[2,5,8–10,16,22,23,26,29–32] There are rare reports of neoplasia in Eurasian otters (*Lutra lutra*)[2,30] and only one reported case of neoplasia, a thyroid adenoma, in a fisher (*Martes pennanti*).[5] Lymphoblastic lymphoma has been reported in one sea otter but has not been documented in any other wild mustelid.[16] This is in remarkable contrast to domestic ferrets (*Mustela putorius furo*), in which neoplasia is frequently diagnosed, with lymphoma being among the most common malignant neoplasms.[13,18] Genetic and infectious causes have been postulated as predisposing factors in the development of lymphoma in ferrets.[3,7] The following is a report of lymphoma of granular lymphocytes (LGL) in a fisher and a Eurasian otter, which is the first in any wild *Mustelidae* to the authors' knowledge.

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CASE REPORTS

Case no. 1

A 5.5-mo-old, nonreleasable male intact fisher was acquired by a zoologic institution in New York after it was hand raised by a wildlife rehabilitator. Yearly physical examinations were performed, and the fisher remained healthy until 6 yr of age, at which time the fisher became progressively hypophagic and lethargic. Vomiting and occasional dark, liquid feces were noted. Fecal samples tested negative for intestinal parasites. Physical examination revealed a poor body condition with a body weight of 3.8 kg, decreased from 6.9 kg 7 mo prior. Peripheral lymph nodes were not enlarged; however, a moveable, firm, irregular, mid to caudal abdominal mass approximately 5 cm in diameter was palpated. Fine-needle aspiration of the mass produced 3 ml of dark red–brown fluid. The fluid and direct smears of solid areas of the mass were submitted to the Animal Health Diagnostic

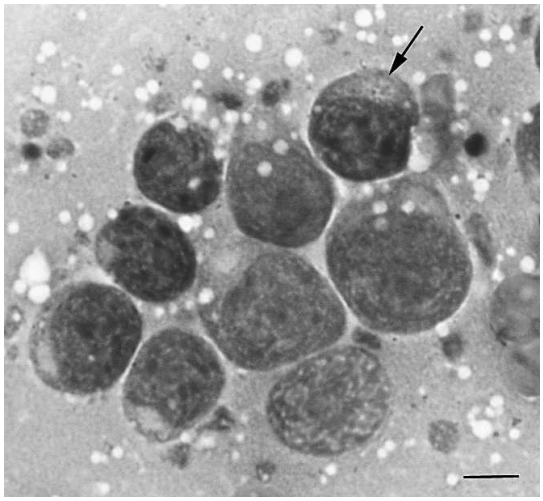

Figure 1. Representative photomicrograph of intermediate to large lymphocytes in an aspirate of a small intestinal mass in a fisher. Small red cytoplasmic granules, located within a perinuclear clear zone, are evident in one of the lymphocytes (arrow). These were present in most of the lymphocytes but were difficult to discern. Wright's stain, bar = 5 μm.

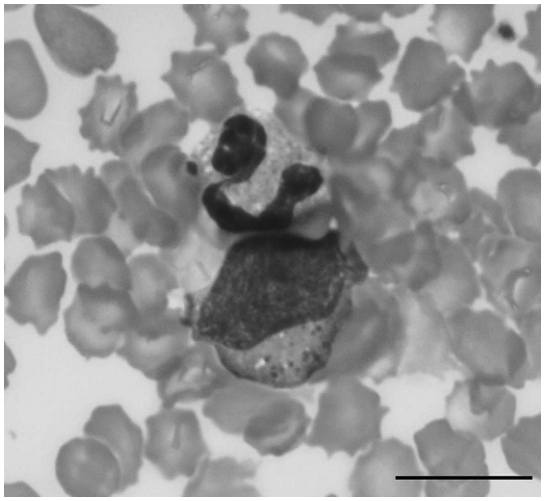

Figure 2. Pictured adjacent to a neutrophil is a large granular lymphocyte with fine red cytoplasmic granules in peripheral blood of a fisher. Wright's stain, bar = 10 μm.

Center at Cornell University for cytologic analysis. Also submitted were whole blood in ethylenediaminetetraacetic acid for a complete blood cell count and heparinized plasma for a biochemistry panel. Cytologic examination of the mass revealed many intermediate to large round cells, with round nuclei, finely stippled chromatin, and one large prominent nucleolus. Low numbers of small (1–2 μm) red to pink cytoplasmic granules were present within the cytoplasm of the majority of cells, frequently localized within the perinuclear clear zone. Due to their small size, the granules were difficult to discern in many cells; however, in several, they were more readily identified (Fig. 1). Occasional mitotic figures were observed. These cells were interpreted as immature granular lymphocytes (GLs). Also present within the smear were low numbers of highly vacuolated macrophages and neutrophils. Direct and sediment smears of the fluid sample revealed a mixed population of bacteria and small amounts of food material. The aspirated fluid was consistent with enterocentesis, and thus a presumptive diagnosis of gastrointestinal LGL was made.

Reference intervals (mean ± 2 SD) for the blood results were acquired from the International Species Information System.[14] The fisher had a normocytic (mean cell volume: 40 fl; reference interval 37–88.2 fl), normochromic (mean corpuscular hemoglobin concentration: 34 g/dl; 24.1–38.1 g/dl) anemia (hematocrit: 25%; 35–55%) with minimal regeneration (reticulocytes: 1%; 0–2%) metarubricytosis (6 nucleated red blood cells/100 white blood cells); a leukocytosis (white blood cells: 23.9 × 10^3/μl; 0.5–9.6 × 10^3/μl) due to a neutrophilia (18.8 × 10^3/μl; 0–5.7 × 10^3/μl), with a mild left shift (1.2 × 10^3/μl; 0–0.2 × 10^3/μl) and mild toxic change; and a monocytosis (1.0 × 10^3/μl; 0–0.4 × 10^3/μl). Although the lymphocyte count was within the reference interval (2.4 × 10^3/μl; 0–4.3 10^3/μl), low numbers of intermediate to large GLs (0.5 × 10^3/μl), similar to that in the abdominal mass aspirate, were seen in the blood smear (Fig. 2). These were interpreted as circulating neoplastic cells, that is, leukemia. Mild red blood cell hypochromasia and fragmentation were also noted during smear examination.

Pertinent abnormal biochemistry results included mild azotemia (urea nitrogen, 40 mg/dL; 7–31 mg/dl), hypoproteinemia (3.5 g/dl; 5.3–7.3 g/dl) due to hypoalbuminemia (1.3 g/dL; 2.7–4.3 g/dl), elevated liver enzymes (alanine aminotransferase, 696 U/L; 0–212 U/L; aspartate aminotransferase, 965 U/L; 15–227 U/L; alkaline phosphatase, 186 U/L; 0–159 U/L; gamma glutamyltransferase, 97 U/L; 0–7 U/L), and hyperbilirubinemia (2.6 mg/dl; 0–1.0 mg/dl, which was mostly direct bilirubin). Due to the advanced nature of the disease, the clinical pathologic results that indicated multiorgan

involvement, and the animal's poor body condition, the fisher was humanely euthanatized.

On necropsy, gross findings included marked loss of body condition, an absence of perirenal and pericardial adipose tissue, and cutaneous icterus. Focally extensive gastrointestinal lesions included a circumferential jejunal mural mass measuring 5 cm × 4 cm × 4 cm, proximal duodenal mural thickening, and an irregularly shaped pyloric mucosal ulcer measuring 2 cm in the greatest dimension. Mesenteric lymphadenomegaly was noted, with the largest node measuring 5 cm × 2 cm × 1 cm. The kidneys were diffusely pale. Representative sections of tissues were fixed in 10% buffered formalin, routinely processed, and stained with hematoxylin and eosin (H&E) for histologic examination. Select neoplastic tissues were stained at two different laboratories with phosphotungstic acid–hematoxylin (PTAH) and periodic acid–Schiff (PAS) techniques. In the affected section of jejunum, the normal architecture was effaced by a nonencapsulated and poorly circumscribed infiltrate of lymphoblasts that extended from the ulcerated mucosal surface to the serosa, effacing all tunics. Neoplastic cells infiltrated between the smooth muscle bundles of the muscularis and extended to the serosal surface in many areas. The cells had scant cytoplasm, vesicular nuclei, prominent nucleoli, and 1–2 mitotic figures per ×400 field (Fig. 3). Cytoplasmic granules were not apparent in histologic sections. Densely cellular aggregates of neoplastic cells, frequently with infiltrates of neutrophils and macrophages, effaced the architecture of mesenteric lymph node and were present throughout the portal areas of the liver, within the interstitium of the testis, and in scattered foci in the renal interstitium. Areas of splenic red pulp were also diffusely infiltrated by neoplastic lymphocytes. The pylorus had an extensive focus of deep mucosal erosion associated with moderate numbers of lymphocytes and plasma cells in the remaining lamina propria, some focal vascular congestion, and edema. No neoplastic cells were identified in the pyloric ulcer, which was attributed to stress. No samples of bone marrow were examined.

In light of the necropsy and histopathology findings, the hematologic and clinical chemistry results were compatible with an iron deficiency anemia due to chronic blood loss from the intestinal ulcer, inflammation, leukemia secondary to the intestinal lymphoma, cholestasis, and hepatic injury (attributed to neoplastic infiltrates). Leukemic infiltrates in the bone marrow and suppression of erythropoiesis by inflammatory cytokines associated with the neoplasm (anemia of inflammatory/chronic disease) could have contributed to the poorly regenerative anemia.

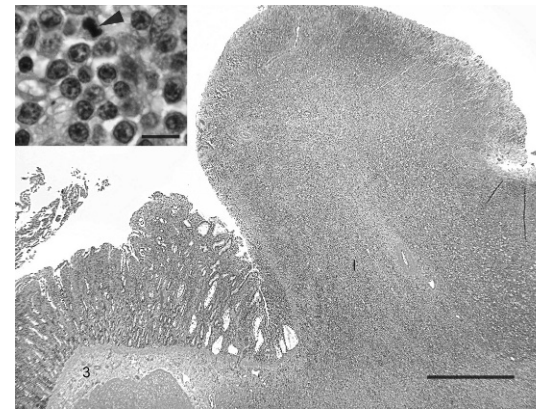

Figure 3. Note thickening of intestinal wall in the fisher due to transmural cellular infiltrate (l) associated with mucosal ulceration. Hematoxylin and eosin (H&E) stain, bar = 560 μm. Inset: Note that neoplastic cells have vesicular nuclei, single prominent nucleoli, and occasional mitoses (arrowhead) and that they lack recognizable intracytoplasmic granules. H&E stain, bar = 20 μm.

Representative sections of tissues containing neoplastic cells were routinely processed for immunohistochemistry.[17] Antigen retrieval was accomplished by incubation of slides in antigen retrieval solution (Dako Corp., Carpinteria, California 93013, USA) in a steamer (Black & Decker, Towson, Maryland 21286, USA) for 20 min. Endogenous peroxidase was blocked for 15 min with 3% hydrogen peroxide. Nonspecific immunoglobulin binding was blocked by incubation of slides for 10 min with a protein-blocking agent (Dako) and then mixed with a primary antibody for 30 min at room temperature. Sections were stained in a Dako autostainer apparatus. The slides were incubated with a mouse monoclonal anti-human CD79a antibody (HM57 B-cells, Dako; dilution of 1:100) and a rat monoclonal anti-canine CD3 antibody (T cells, Peter Moore, dilution 1:10). A streptavidin-biotin-immunoperoxidase staining procedure (Dako) was used for immunolabeling. The immunoreaction was visualized with 3, 3′-diaminobenzidine substrate (Dako). Sections were counterstained with Mayer's hematoxylin. Positive immunohistochemical controls included normal canine and ferret lymph node, to which the appropriate antisera were added. Internal control

tissue was also utilized. For negative controls, the primary antibodies were replaced with homologous nonimmune sera. Neoplastic cells had positive membranous immunoreactivity to CD3 and were negative for CD79a, consistent with a diagnosis of T-cell lymphoma, likely of primary alimentary origin.

Case no. 2

A captive geriatric male Eurasian otter at a zoologic institution in California was presented for acute onset of lethargy and inappetance. The otter had a previous history of azotemia and abdominal pain that was attributed to unilateral nephrolithiasis. A few months before terminal presentation, an abdominal ultrasound and a unilateral nephrectomy were performed, during which no intestinal abnormalities were detected. Due to concerns about quality of life, euthanasia was elected; therefore, no clinical workup was performed, and no clinical data were collected.

On gross necropsy, the peritoneal cavity contained 300–400 ml of yellow cloudy fluid. Serosal surfaces were diffusely dull, granular, and multifocally covered with small amounts of fibrin. The small intestine was segmentally thickened in two regions with a single perforation through the wall at the mesenteric aspect of the larger segment. This segment, 4 cm in length, was in the mid-jejunum. The smaller segment, 2.5 cm in length, was in the distal jejunum. In both sections, the wall of the intestine was circumferentially thickened, varying from 1 to 1.5 cm wide. On cut section, the affected wall was homogenous, soft, tan, and bulging and lacked distinction between muscular wall, submucosa, and mucosa. A direct impression of one of the intestinal masses revealed large lymphocytes containing brightly eosinophilic cytoplasmic granules (Fig. 4). Additional gross findings included moderate right ventricular dilation; mild hydrocephalus; focal chronic splenic infarction; and poor body condition, as indicated by minimal to absent perirenal and pericardial adipose tissue.

A complete routine set of tissue samples, including numerous sections of the intestinal masses, were collected and fixed in 10% buffered formalin. Tissue samples were routinely processed, embedded in paraffin, cut in 5-μm-thick sections, and stained with H&E. As with the fisher, select paraffin-embedded, formalin-fixed sections of the intestinal masses were additionally stained with PTAH and PAS. Histologically, similar findings, although of varying severity, were found in all sections of the intestinal masses examined. In the most severely affected section near the perforation, the normal intestinal architecture was diffusely replaced by a circumferential transmural infiltrate of homogenous neoplastic lymphocytes that extended from the mucosal surface, through the muscular wall, and into the attached mesentery. The neoplastic cells formed broad sheets to occasional streams between smooth muscle bundles, small blood vessels, and fine connective tissue stroma. The cells had scant cytoplasm, round to rhomboidal granular nuclei, and occasional single nucleoli and mild anisokaryosis. Mitotic figures were present at 5–6 per high-power field (×400). Throughout the section examined, the mucosal epithelium was absent, replaced by abundant fibrin and degenerate neutrophils and macrophages. The serosa was covered by fibrin, macrophages, and few neutrophils, consistent with acute peritonitis secondary to the acute focal perforation. Cytoplasmic granules were not apparent in histologic sections stained with H&E and PTAH, although rare neoplastic cells had PAS-positive granules. No metastatic or leukemic disease was noted in any of the other tissues examined histologically. Additional findings were interpreted as reactive, geriatric, or incidental and included serous atrophy of fat, moderate multifocal myocardial fibrosis, moderate portal fibrosis, bile duct hyperplasia and hepatocellular lipidosis, moderate lipid pneumonia, mild membranoproliferative glomerulonephritis, single adrenocortical adenoma with diffuse cortical ade-

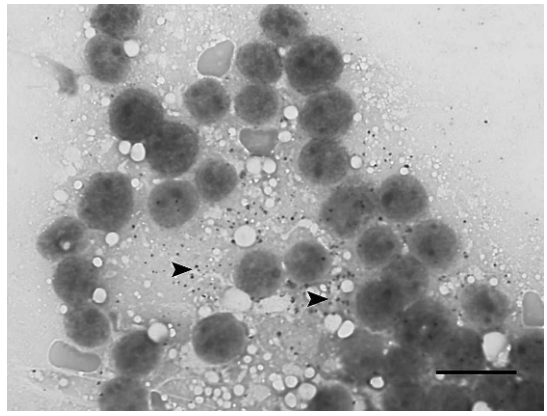

Figure 4. Direct impression of the cut surface of the distal jejunal mass of the Eurasian otter demonstrating brightly eosinophilic granules (arrow heads) in the cytoplasm of neoplastic lymphocytes. The cytoplasm is rarely intact, and nuclei exhibit moderate anisokaryosis with frequent multiple nucleoli. Diff-Quik stain, bar = 10 μm.

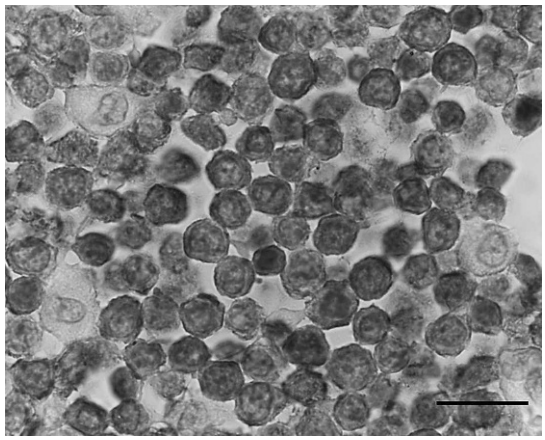

Figure 5. The neoplastic lymphocytes from the distal jejunal mass of the Eurasian otter exhibit moderate to strong membrane immunoreactivity to CD3, consistent with a T-cell immunophenotype. The chromogen used for visualization of positive immunoreactivity was 3, 3′-diaminobenzidine. Bar = 10 μm.

nomatous hyperplasia, multiple thyrofollicular cystadenomas, and marked nontapetal retinal atrophy.

Immunohistochemistry for rat −CD3ε (clone CD3-12, Serotec, Raleigh, North Carolina 27606, USA) and CD79a (clone HM57, Dako) was performed on a section of small intestine. Spleen from an unrelated Eurasian otter was used as a positive control. Neoplastic lymphocytes were diffusely immunoreactive for CD3 (Fig. 5). Immunoreactivity was absent for CD79a.

In this case, the diagnosis of LGL was made based on the presence of a monomorphic population of neoplastic lymphocytes infiltrating segments of the small intestine, the presence of intracytoplasmic eosinophilic granules within these cells, and the CD3+, CD79a− immunophenotype. The granules could only be easily visualized on cytology from a direct impression of affected intestine. The affected segments of intestine were in the mid- and distal jejunum. The clinical behavior appeared aggressive, with progression to grossly observable disease and perforation occurring within a few months after the intestinal tract had been evaluated as normal by ultrasound examination and abdominal exploration. No abnormal or neoplastic lymphocytes were observed in peripheral blood smears that were performed in previous clinical workups.

DISCUSSION

Granular lymphocytes are normally present within the intestinal epithelium and can make up between 5 and 10% of lymphocytes in peripheral blood of different species.[1,21] Neoplasia of granular lymphocytes can present as lymphoma or primary leukemia. Although uncommon, neoplasia of GLs has been documented in humans, cats, dogs, rats, horses, a calf, and a ferret.[4,6,12,15,19–21,24,25,27,28] Of these, the tumor in the fisher and otter most closely resembled that seen in cats. Large granular lymphoma in cats is characterized by clinically aggressive behavior and primary small intestinal involvement with or without leukemia.[27] Neoplastic infiltration of the mesenteric lymph nodes, liver, spleen, and other organs can occur. Large granular lymphoma has a poor prognosis, which is often due to advanced disease at the time of diagnosis.[27]

Although cytoplasmic granules were detected in cytologic preparations of the neoplastic population in the fisher and otter, these granules were not seen in most histologic sections. Rare neoplastic cells in the Eurasian otter inconsistently had PAS-positive granules. The difficulty in visualizing granules in histologic sections stained with H&E has been noted in other species, and the effectiveness of PTAH and PAS to better demonstrate these granules is variable.[4,6,12,24,25,27,28] This is in contrast to the ease of demonstrating granules in cytologic preparations.[4,27,28] Some authors contend that accurate diagnosis of LGL requires cytology of tissue and peripheral blood due to the difficulty in identifying neoplastic cells in routinely stained tissue sections.[27] The absence of granules in histologic sections in these cases should not, therefore, preclude the diagnosis.

In humans, GLs can derive from cytotoxic T cells or natural killer cells. These are differentiated from each other based in part on their expression of CD3 surface antigen; typically cytotoxic T-cell GLs are CD3 positive, and natural killer–cell GLs are negative.[20] Specific cross-reactivity of anti-CD3 antibodies with ferret lymphoid tissue for immunohistochemistry has been documented.[11] Although this antibody has not been validated for fishers or Eurasian otters, appropriate immunoreactivity of CD3 and CD79a was observed in control tissues (periartiolar lymphoid sheath and lymphoid follicles, respectively) from an unaffected Eurasian otter (Imai, pers. comm.). Although controls were not available for the fisher, cross-reactivity of the monoclonal antibodies to CD3 and CD79a is possible if leukocyte cell surface antigens are conserved across the *Mustelidae* family. In the cases presented in this report, the tumors were

positive for CD3, confirming a T-cell origin. Similarly, the vast majority of LGLs or leukemias of granular lymphocytes are due to neoplastic proliferation of T-cells in cats and dogs.[21,27]

In conclusion, LGLs in the fisher and Eurasian otter discussed in this report was clinically aggressive and behaved similarly to those seen in domestic felids. The diagnosis often carries a poor prognosis. To make an accurate diagnosis, clinicians and pathologists should perform cytology on fresh tissue, because granules are difficult or impossible to detect in fixed tissues. Although special stains, including PAS and PTAH, have enhanced visualization of granules in other species, they were not of benefit in the wild mustelids in this report.

LITERATURE CITED

1. Alberti, S., F. Colotta, F. Spreafico, D. Delia, E. Pasqualetto, and W. Luini. 1985. Large granular lymphocytes from murine blood and intestinal epithelium: comparison of surface antigens, natural killer activity, and morphology. Clin. Immunol. Immunopathol. 36: 227–238.

2. Bae, I. H., B. Pakhrin, H. Jee, N. S. Shin, and D. Y. Kim. 2007. Hepatocellular adenoma in a Eurasian otter (*Lutra lutra*). J. Vet. Sci. 8: 103–105.

3. Batchelder, M. A., S. E. Erdman, X. Li, and J. G. Fox. 1996. A cluster of cases of juvenile mediastinal lymphoma in a ferret colony. Lab. Anim. Sci. 46: 271–274.

4. Boone, L. I., R. Barthel, R. G. Helman, and M. Drew. 1995. Large granular lymphocyte leukemia in a ferret. Vet. Clin. Pathol. 24: 6–10.

5. Carlson, B. L., and S. W. Nielsen. 1985. Thyroid adenoma and ovarian luteinization in an aged fisher (*Martes pennanti*). J. Wildl. Dis. 21: 320–324.

6. Darbes, J., M. Majzoub, W. Breuer, and W. Hermanns. 1998. Large granular lymphocyte leukemia/lymphoma in six cats. Vet. Pathol. 35: 370–379.

7. Erdman, S. E., K. A. Reimann, F. M. Moore, P. J. Kanki, Q. Yu, and J. G. Fox. 1995. Transmission of a chronic lymphoproliferative syndrome in ferrets. Lab. Investig. 72: 539–546.

8. Hadlow, W. J. 1984. Vertebral chordoma in two ranch mink. Vet. Pathol. 21: 533–536.

9. Hadlow, W. J. 1985. Carcinoma of the anal sac glands in ranch mink. Vet. Pathol. 22: 206–218.

10. Hadlow, W. J. 1986. Carotid body tumor: an incidental finding in older ranch mink. Vet. Pathol. 23: 162–169.

11. Hammer, A. S., B. Williams, H. H. Dietz, and S. J. Hamilton-Dutoit. 2007. High-throughput immunophenotyping of 43 ferret lymphomas using tissue microarray technology. Vet. Pathol. 44: 196–203.

12. Herraez, P., B. Berridge, P. Marsh, B. Weeks, and F. Ramiro-Ibanez. 2001. Small intestine large granular lymphoma in a horse. Vet. Pathol. 38: 223–226.

13. Hess, L. 2005. Ferret lymphoma: the old and the new. Semin. Avian Exot. Pet Med. 14: 199–204.

14. International Species Inventory System. 2002. Physiological Reference Values for *Martes pennanti*. CD-ROM. International Species Inventory System. Apple Valley, Minnesota.

15. Jacobs, R. M., J. B. Messick, and V. E. Valli. 2002. Tumors of the hemolymphatic system. *In:* Meuten, D. J. (ed.). Tumors of Domestic Animals, 4th ed. Blackwell Publishing, Ames, Iowa. Pp. 119–198.

16. Kim, J. H., B. H. Kim, J. H. Kim, M. J. Yoo, and D. Y. Kim. 2002. Lymphosarcoma in a sea otter (*Enhydra lutris*). J. Wildl. Dis. 38: 616–617.

17. Kiupel, M., D. Bostock, and E. Teske. 1999. Prognostic factors for the treatment of canine malignant lymphoma. Vet. Pathol. 36: 292–230.

18. Li, X., J. G. Fox, and P. A. Padrid. 1998. Neoplastic diseases in ferrets: 574 cases (1968–1997). J. Am. Vet. Med. Assoc. 212: 1402–1406.

19. Losco, P. E., and J. M. Ward. 1984. The early stage of large granular lymphocyte leukemia in the F344 rat. Vet. Pathol. 21: 286–291.

20. Loughran, T. P. 1993. Clonal diseases of large granular lymphocytes. Blood. 82: 1–14.

21. McDonough, S. P., and P. F. Moore. 2000. Clinical, hematologic, and immunophenotypic characterization of canine large granular lymphocytosis. Vet. Pathol. 37: 637–646.

22. Mikaelian, I., B. Martineau-Doize, and D. Martineau. 1998. Giant-cell osteosarcoma in a female ranch mink (*Mustela vison*). J. Vet. Diagn. Invest. 10: 301–302.

23. Nakamura, K., H. Tanimura, K. Katsuragi, T. Shibahara, and K. Kodata. 2002. Differentiated basal cell carcinoma in a Cape clawless otter (*Aonyx capensis*). J. Comp. Path. 127: 223–227.

24. Nozaki, S., K. Sasaki, M. Ando, and K. Kadota. 2006. Natural killer–like T-cell lymphoma in a calf. J. Comp. Pathol. 135: 47–51.

25. Quist, C. F., B. G. Harmon, E. A. Mahaffey, and C. Collatos. 1994. Large granular lymphocyte neoplasia in an aged mare. J. Vet. Diagn. Invest. 6: 111–113.

26. Reimer, D. C., and T. P. Lipscomb. 1998. Malignant seminoma with metastasis and herpesvirus infection in a free-living sea otter (*Enhydra lutris*). J. Zoo Wildl. Med. 29: 35–39.

27. Roccabianca, P., W. Vernau, M. Caniatti, and P. F. Moore. 2006. Feline large granular lymphocyte (LGL) lymphoma with secondary leukemia: primary intestinal origin with predominance of a CD3/CD8$\alpha\alpha$ phenotype. Vet. Pathol. 43: 15–28.

28. Snead, E. C. R. 2007. Large granular intestinal lymphosarcoma and leukemia in a dog. Can. Vet. J. 48: 848–851.

29. Stetzer, E., T. D. Williams, and J. W. Nightingale. 1981. Cholangiocellular adenocarcinoma, leiomyoma, and pheochromocytoma in a sea otter. J. Am. Vet. Med. Assoc. 179: 1283–1284.

30. Weber H., and L. Mecklenburg. 2000. Malignant melanoma in a Eurasian otter (*Lutra lutra*). J. Zoo Wildl. Med. 31: 87–90.

31. Williams, T. D., and L. T. Pulley. 1981. Leiomyomas in two sea otters, *Enhydra lutris*. J. Wildl. Dis. 17: 401–404.

32. Zachary, J. F., and S. C. McDonald. 1981. Malignant ovarian teratoma in a spot-neck otter. J. Am. Vet. Med. Assoc. 179: 1279–1283.

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