IMAGING FINDINGS IN 14 DOMESTIC FERRETS (*MUSTELA PUTORIUS FURO*) WITH LYMPHOMA

JANTRA NGOSUWAN SURAN, NICOLE RENE WYRE

Lymphoma is the most common malignant neoplasia in domestic ferrets, *Mustela putorius furo*. However, imaging findings in ferrets with lymphoma have primarily been described in single case reports. The purpose of this retrospective study was to describe imaging findings in a group of ferrets with confirmed lymphoma. Medical records were searched between 2002 and 2012. A total of 14 ferrets were included. Radiographs ($n = 12$), ultrasound ($n = 14$), computed tomography (CT; $n = 1$), and magnetic resonance imaging (MRI; $n = 1$) images were available for review. Median age at the time of diagnosis was 5.2 years (range 3.25–7.6 years). Clinical signs were predominantly nonspecific (8/14). The time between the first imaging study and lymphoma diagnosis was 1 day or less in most ferrets (12). Imaging lesions were predominantly detected in the abdomen, and most frequently included intra-abdominal lymphadenopathy (12/14), splenomegaly (8/14), and peritoneal effusion (11/14). Lymphadenopathy and mass lesions were typically hypoechoic on ultrasound. Mild peritoneal effusion was the only detected abnormality in two ferrets. Mild pleural effusion was the most common thoracic abnormality (3/12). Expansile lytic lesions were present in the vertebrae of two ferrets with T3-L3 myelopathy and the femur in a ferret with lameness. Hyperattenuating, enhancing masses with secondary spinal cord compression were associated with vertebral lysis in CT images of one ferret. The MRI study in one ferret with myelopathy was inconclusive. Findings indicated that imaging characteristics of lymphoma in ferrets are similar to those previously reported in dogs, cats, and humans. © 2013 *Veterinary Radiology & Ultrasound.*

Key words: computed tomography, CT, ferret, lymphoma, lymphosarcoma, lymphoproliferative, magnetic resonance imaging, MRI, radiograph, ultrasound.

Introduction

LYMPHOMA IS the most common malignant neoplasia in domestic ferrets, *Mustela putorius furo*. Following insulinoma and adrenocortical neoplasia, it is the third most common neoplasia of domestic ferrets overall.[1–4] In ferrets, lymphoma can be classified based on tissue involvement, including multicentric, mediastinal, gastrointestinal, cutaneous, and extranodal.[1–3] The presentation and organ distribution of lymphoma has been associated with the age of onset.[5,6] Mediastinal lymphoma is more prevalent in young ferrets, particularly less than 1 year of age. These ferrets tend to have an acute presentation and may present with dyspnea. Ferrets with mediastinal lymphoma may also have multicentric involvement.[2,5,6] Ferrets 3 years of age and greater have a variable presentation with multicentric disease being more prevalent. Clinical signs in older ferrets may be chronic and nonspecific depending on organ involvement. Some ferrets may have intermittent signs over several months, while others may be asymptomatic with lymphoma being diagnosed incidentally, detected either during routine physical examination or during evaluation of comorbidities.[1–3]

Despite lymphoma being common in domestic ferrets and the use of radiography and ultrasonography being touted as part of the minimum database in the diagnosis of lymphoma,[1,7] imaging findings in ferrets with lymphoma have been limited to a few case reports.[1,2,5,6,8–11] The goal of this retrospective study was to describe radiography, ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) findings in a series of ferrets with a confirmed diagnosis of lymphoma.

Material and Methods

Medical records at the Matthew J Ryan Veterinary Hospital of the University of Pennsylvania were searched for domestic ferrets with a diagnosis of lymphoma confirmed with cytology or histopathology that had radiography, ultrasonography, CT, or MRI performed between January 2002 and April 2012. Signalment, clinical signs, laboratory findings, and any prior or concurrent disease processes were recorded.

From the Sections of Radiology (Suran) and Exotic Companion Animal Medicine and Surgery (Wyre), Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, 3900 Delancey Street, Philadelphia, PA 19104.

Address correspondence and reprint requests to Jantra N. Suran, at the above address. E-mail: jsuran@vet.upenn.edu

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Radiographs, CT, MRI, static ultrasound images, and when available, ultrasound cine loops were retrospectively evaluated, and abnormal findings were recorded by J.N.S. The imaging reports generated by a board-certified veterinary radiologist at the time the study was performed were also reviewed. Ferrets were excluded if the imaging studies were unavailable for review. Any imaging studies obtained after the reported start of clinical signs until a diagnosis was achieved were included. In addition to the reported ultrasonographic findings, the maximal splenic and lymph node thicknesses were measured from the available images if they were not reported. As splenomegaly is common in ferrets, most frequently due to extramedullary hematopoiesis,[2] splenomegaly was subjectively graded as within incidental variation ("incidental splenomegaly") and larger than expected for "incidental splenomegaly." Those with subjectively normal spleens or "incidental splenomegaly" were referred to as normal for the purposes of this paper, unless otherwise specified. Retrieved CT images were reconstructed with a high-frequency high-resolution algorithm (bone algorithm with edge enhancement) in 1.25 mm slice thickness. The maximal lymph node thickness was measured on precontrast images.

Results

Fourteen ferrets met the inclusion criteria. Lymphoma was diagnosed from ultrasound-guided aspirates, surgical biopsies, and/or necropsy; three ferrets had two diagnostic procedures performed. Ultrasound-guided aspirate cytology was performed in nine ferrets, surgical biopsy in three, and necropsy in five. Both aspirates and biopsy were performed in two ferrets, and both aspirates and necropsy in one ferret. One ferret in this study was previously described.[8] The median age at the time of lymphoma diagnosis was 5.2 years (range 3.25–7.6 years). Eight of the ferrets were neutered males, and six were spayed females. Prior disease histories included adrenal disease ($n = 5$), cardiovascular disease (5), cutaneous mast cell tumors (4), diarrhea (3), insulinoma (2), cataracts (2), and one each of granulomatous lymphadenitis secondary to mycobacteriosis, renal insufficiency, and a chronic pelvic limb abscess. Cardiovascular disease included second degree atrioventricular block (3), systemic hypertension (1), hypertrophic obstructive cardiomyopathy (1), and in one individual both aortic insufficiency and arteriosclerosis. For most ferrets, the time between the first imaging study and a diagnosis of lymphoma was 1 day or less (12/14). In one ferret each, the time between the initial imaging study and final diagnosis of lymphoma was 7 days and 6.9 months. The duration of clinical signs prior to reaching the diagnosis of lymphoma ranged from less than 1 day to 8 months with a mode of less than 1 day and a median of 6 days. Clinical signs include lethargy ($n = 9$), diarrhea (8), inappetence (7), weight loss (6), ataxia (4), lameness (1), and vomiting (1). Diarrhea was chronic in three ferrets and consistent with melena in two. Two ferrets did not have overt clinical signs.

Physical exam findings included palpable abdominal masses (8), generalized splenomegaly (5), palpable splenic nodules or splenic masses (3), dehydration (5), paraparesis and ataxia (4), abdominal pain (4), hypotension (3), lumbar pain (2), abdominal effusion (1), inguinal and popliteal lymphadenopathy (1), pyrexia (1), urinary and fecal incontinence (1), and a right femoral mass (1). Paraparesis and ataxia were attributed to T3-L3 myelopathy in three ferrets and hypoglycemia in one. One ferret also presented with ptyalism and tremors, which resolved with dextrose administration. Blood analyses, including a complete blood count and chemistry profile, were performed in 12 of the 14 ferrets. Blood glucose evaluation alone was performed in one ferret. Abnormalities included azotemia (5), elevated liver enzymes (5), nonregenerative anemia (4), hypoglycemia (4), hypoalbuminemia (3), lymphocytosis (2), hyperglobulinemia (2), hypercalcemia (1), and elevated total bilirubin (1). Two of the four ferrets with hypoglycemia had a previous diagnosis of insulinoma.

Radiographs were performed in 12/14 ferrets. Each of these 12 studies included the thorax and abdomen—six studies included a right or left lateral projection and a ventrodorsal projection and six included a left lateral, right lateral, and ventrodorsal projections. One ferret's radiographs were in an analog format (screen-film), and the remaining 11 were digital (RapidStudy, Eklin Medical Systems Inc., Santa Clara, CA). Ultrasound was performed in 14/14 ferrets using a 13–15 MHz linear transducer (GE Medical LOGIQ 9 Ultrasound Imaging System, General Electric Medical Systems, Milwaukee, WI).

Abdominal ultrasonography was performed in 13/14 ferrets. Ultrasonography of a rib mass and a femoral mass was performed in one ferret each. Abdominal ultrasonography was performed twice in one ferret after the start of the reported clinical signs, but prior to the diagnosis of lymphoma. Ultrasounds were performed by a board-certified radiologist or a radiology resident under direct supervision from a board-certified radiologist. In the one ferret with two ultrasounds performed prior to diagnosis of lymphoma, the later scan was used for measurements. Computed tomography of the thorax and abdomen was performed in one ferret. The ferret was scanned under general anesthesia in dorsal recumbency using a 16-slice multidetector CT unit (GE BrightSpeed, General Electric Company, Milwaukee, WI) in medium-frequency soft tissue algorithms (2.5 mm slice thickness, 1.375 pitch) before and immediately after IV administration of nonionic iodinated contrast (iohexol, 350 mgI/ml, dosage 770 mgI/kg, [Omnipaque, GE Healthcare, Inc., Princeton, NJ]). Contrast was manually injected through an IV catheter preplaced in a cephalic vein. One

TABLE 1. Summary of Whole Body Radiography ($n = 12$) and Abdominal Ultrasound Findings ($n = 13$) in Ferrets with Lymphoma

Location	Modality	Findings	All (*n*)	Lymphoma Confirmed (*n*)
Abdomen				
Peritoneum	R	Decreased serosal detail	10	
		Mottled serosal detail	7	
	US	Peritoneal effusion	11	1
Spleen	R	Normal	5	1
		Enlarged	7	4
	US	Normal	5	1
		Mottled echotexture, enlarged	1	
		Nodules, enlarged	6	3
		Mass, enlarged	1	
Lymph nodes	R	Enlarged or mass-like	7	4
	US	Abnormal (hypoechoic, rounded, variably enlarged)	11	6
Liver	R	Mild hepatomegaly	5	
	US	Normal	10	1
		Mild hepatomegaly	1	1
		Moderate hepatomegaly and hypoechoic, mottled echotexture	1	
		Hypoechoic cystic masses	1	
Gastrointestinal	R	Normal	12	1
	US	Normal	12	1
		Gastric thickening	1	1
Kidneys	US	Hypoechoic mass	2	1 (1 sarcoma)
Retroperitoneum	R/US	Mass	1	1
Thorax				
Pleural effusion	R/US		4	
Pericardial effusion	US		1	
Musculoskeletal				
Vertebrae	R	Expansile lysis	2	1
Rib	R	Expansile lysis	1	1
Femur	R	Expansile lysis	1	1

R, radiograph; US, abdominal ultrasound; *n*, number.

ferret underwent MRI evaluation of the lumbar and sacral spine. Magnetic resonance imaging was performed using a 1.5 T MRI unit (GE Medical System, Milwaukee, WI) with the patient in dorsal recumbency under general anesthesia. Image sequences included T2 weighted (T2w) image series in a sagittal and transverse plane, T2w fat-saturated images in a sagittal and transverse plane, and a sagittal single-shot fast spine echo. Additional sequences including T1 weighted (T1w) images and administration of gadolinium were not performed due to anesthetic concerns for the patient.

Radiographic and ultrasonographic findings are summarized in Table 1. Radiographic abnormalities were predominantly noted in the abdomen. Decreased abdominal serosal detail was present in 10 of the 12 ferrets with radiographs. This was interpreted to be potentially due to a poor body condition in two ferrets. Abdominal serosal detail was additionally mottled in seven ferrets. Sonographically, peritoneal effusion was detected in 11/13 ferrets, and was considered mild in 7, moderate in 4, anechoic in 8, and echogenic in 3. The spleen was considered enlarged in 7 out of 12 ferrets radiographically and in 8 out of 13 ferrets in which abdominal ultrasonography was performed. The remaining five ferrets were considered to have "incidental splenomegaly" on ultrasound and were radiographically considered normal ($n = 4$) and enlarged (1). Of the eight spleens sonographically considered abnormal, multifocal hypoechoic splenic nodules were present in six ferrets (Fig. 1); one of these six ferrets was considered to have a radiographically normal spleen. An isoechoic to hypoechoic mass with central hypoechoic nodules was present in one ferret. The spleen had a mottled echotexture in one ferret. Three ferrets were sedated with butorphanol

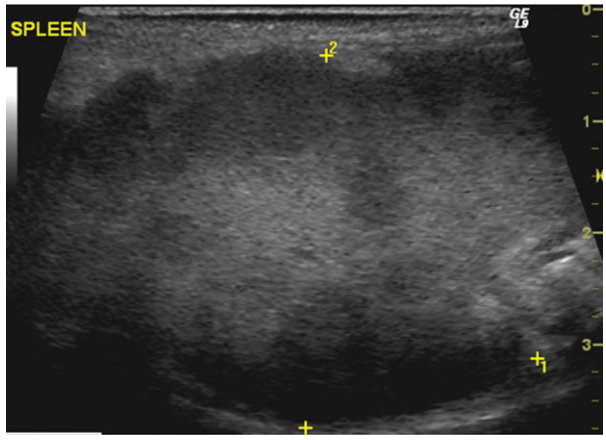

FIG. 1. Ultrasound image of an enlarged spleen with multifocal, ill-defined, hypoechoic nodules. The calipers (+) are at the margins of the spleen.

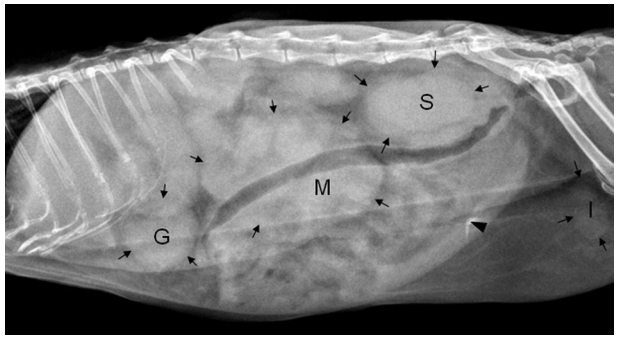

FIG. 2. Right lateral abdominal radiograph. There are multiple, oblong, soft-tissue masses (arrows) consistent with enlarged lymph nodes. Serosal detail is mottled. Wet hair artifact (arrow head) is superimposed on the caudal abdomen. G, gastroduodenal lymph node; M, mesenteric lymph nodes; S, sublumbar lymph nodes; I, inguinal lymph node.

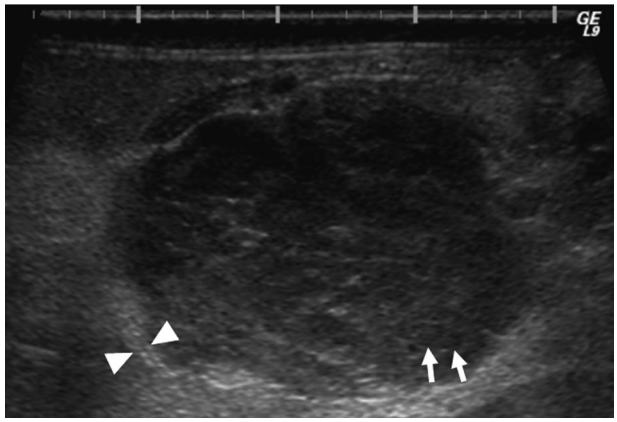

FIG. 3. Ultrasound image of an enlarged hepatic lymph node in the same ferret as Fig. 2. The hepatic lymph node is markedly enlarged and lobular. Although the node is predominantly hypoechoic, there are patchy hyperechoic regions and smaller, round, hypoechoic, nodule-like regions within (arrow). The surrounding fat is hyperechoic, producing a halo around the lymph node (arrow heads). Scale at the top of the image is 10 mm between the major ticks.

(Torbugesic, Fort Dodge Animal Health, Fort Dodge, IA) and midazolam (Hospira Inc., Lake Forrest, IL) prior to abdominal ultrasonography; sedation was not performed in any ferret prior to radiographs. All three sedated ferrets had enlarged spleens with one spleen having a mottled echotexture and the other two spleens having multifocal hypoechoic nodules. Splenic cytology or histopathology was not performed in any of the ferrets that received sedation for ultrasound. Cytology or histopathology was available in seven ferrets—aspirates were performed in 2/7, necropsy in 4/7, and both aspirates and necropsy in 1/7. Lymphoma was confirmed in three out of six ferrets with splenic nodules, the one ferret with a splenic mass, and one out of five ferrets with "incidental splenomegaly." In three of the five ferrets with "incidental splenomegaly," marked splenic extramedullary hematopoiesis with splenic congestion (1) and without concurrent splenic congestion (1) was diagnosed. The other seven ferrets did not have cytologic evaluation of the spleen. Splenic thickness in ferrets where the spleen was considered within incidental variation ranged from 8.0 to 16.2 mm (median, 15.0 mm, mean 13.4 mm, standard deviation ±3.5 mm; $n = 5$), while in ferrets with splenomegaly splenic thickness ranged from 14.2 to 33.1 mm (median 19.9 mm, mean 20.9 mm, standard deviation ±6.4 mm; $n = 8$).

Single or multiple, round to oblong, soft-tissue opaque, abdominal masses consistent with enlarged lymph nodes were visible radiographically in 7/12 ferrets (Fig. 2). One of these ferrets had a large cranial abdominal mass, which was subsequently confirmed to be a markedly enlarged pancreatic lymph node. One ferret had splenic lymphadenopathy detected on the radiographs retrospectively after evaluation of the sonographic findings. Lymphadenopathy was reported in 11 of the 13 ferrets with abdominal ultrasonography and the one ferret in which whole body CT was performed. Sonographically, abnormal lymph nodes were hypoechoic, rounded, variably enlarged, and surrounded by a hyperechoic rim (Fig. 3). Some lymph nodes had patchy hyperechoic regions within or a reticular, nodular appearance. Abdominal lymph nodes involved included the mesenteric ($n = 10$), hepatic (7), sublumbar (5), splenic (4), gastric (3), gastroduodenal (3), colonic (3), pancreatic (2), ileocolic (1), renal (1), and inguinal (1) lymph nodes. In one ferret other lymph nodes were reported to be involved in addition to the mesenteric and sublumbar nodes, but were not specifically identified. Nine of the 11 ferrets with abdominal ultrasound and the one ferret with CT had involvement of 2 or more lymph nodes reported; 2/11 ferrets had only one reportedly abnormal lymph node (1 splenic lymph node, 1 mesenteric lymph node). Lymph nodes measured from 4.8 to 29.5 mm thick (median 8.5, mean 11.6 mm, standard deviation ±8.1 mm). The lymph node thickness in ferrets with radiographically evident lymphadenopathy ranged from 6.2 mm to 29.5 mm with a median of 9.7, and mean of 14.5, and standard deviation of ±9.7 mm ($n = 7$). In ferrets in which lymphadenopathy was detected sonographically but not radiographically, lymph nodes measured 4.8 mm, 5.2 mm, and 11.7 mm thick ($n = 3$). Lymph node cytology or histopathology was available in seven ferrets—aspirates were performed in 3/7 ferrets, both aspirates and surgical biopsy in 1/7, and necropsy in 3/7. It was not clear if lymph nodes were histopathologically assessed in 2/5 ferrets in which a necropsy was performed. Lymphoma was confirmed in 6/11 ferrets with sonographically abnormal lymph nodes (range 5.2–29.5 mm thick, median 14.8 mm, mean ± standard deviation 17.2 ± 9.3 mm). In 1/11 ferrets, lymphoid hyperplasia was identified postmortem (6.2 mm thick). Cytologic evaluation of lymph nodes was not performed in the remaining ferrets. In ferrets with lymphadenopathy, eight had concurrent splenomegaly with

FIG. 4. Ultrasound image of the gastric antrum. The wall of the gastric antrum, especially the muscularis layer, is circumferentially thickened (arrows). A small amount of fluid and gas (*) is present in the lumen.

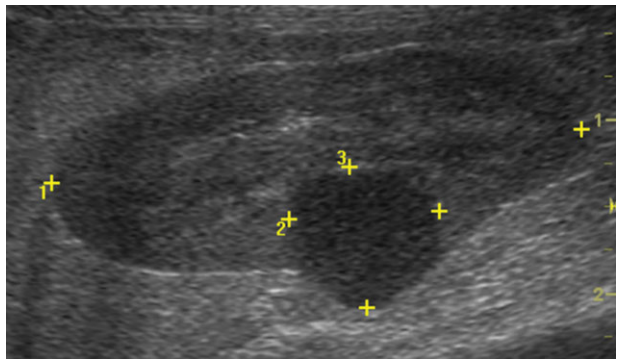

FIG. 5. Ultrasound image of the right kidney. There is a round, hypoechoic nodule in the parenchyma, which bulges from the renal contour. The calipers (+) denote the renal length (1) and margins of the nodule (2, 3).

splenic nodules (6), a splenic mass (1), or a mottled splenic echotexture (1).

Lymphoma was identified in the liver of 2/14 ferrets by surgical biopsy (1) and at necropsy (1). Mild hepatomegaly with a normal echotexture was noted on ultrasound in the ferret with lymphoma diagnosed by biopsy. Additional findings in this ferret included mild peritoneal effusion and lymphadenopathy. The ferret with hepatic lymphoma identified at necropsy had no radiographic or reported sonographic liver abnormalities. This ferret also had hepatic lipidosis. Imaging findings in this ferret included an aggressive vertebral lesion, splenomegaly with splenic nodules, and lymphadenopathy. Lymphoma was confirmed in each of these organs, as well as in the pancreas, which was reportedly normal on ultrasound. In addition to these two ferrets, hepatic histopathology from necropsy was available in four other ferrets. Hepatic lipidosis was identified each of these four ferrets; one ferret also had extramedullary hematopoiesis. None of these four ferrets had radiographic or reported sonographic abnormalities. Cytology or histopathology was not available in the remaining 8/14 ferrets. Of these, 1/8 had no radiographic or sonographic abnormalities noted. Mild hepatomegaly was noted radiographically in 5/8 ferrets; however, sonographic hepatic changes were not noted in these ferrets and cytologic evaluation was not performed. On ultrasound, one ferret had moderate hepatomegaly with a hypoechoic, mottled echotexture (radiography was not performed in this ferret). Additionally one ferret had two hypoechoic cystic masses, one mass of which had central mineralization, detected with ultrasound (radiography was not performed in this ferret).

Gastrointestinal lymphoma was confirmed at necropsy in two ferrets. In one ferret, thickening of the gastric antrum up to 4.5 mm and blurring of wall layering was identified sonographically (Fig. 4). (To the authors' knowledge, the normal gross or sonographic wall thickness of the gastrointestinal tract in ferrets has not been previously reported.) No abnormalities were noted in the small or large intestines. At necropsy, lymphoma was identified in the stomach and small intestines, in addition to a chronic ulcerative gastroenteritis. In the second ferret, aside from poor abdominal serosal detail attributable to poor body condition and mild anechoic peritoneal effusion, there were no other radiographic or sonographic abnormalities. In this ferret, lymphoma was identified postmortem in the descending colon. The colon was discolored, but there was no reported gross colonic wall thickening.

Renal masses were present in two ferrets. In each ferret, a single renal mass was detected with ultrasound and was well defined, hypoechoic, centered on the cortex, and protruded from the kidney. The mass was right-sided, rounded, and measured 8.6 mm in diameter in one of these two ferrets. In the second ferret, the mass was left-sided, lobular, and measured up to 17.9 mm in diameter. Cytology of the right renal mass in the first ferret was not performed; however, the patient received chemotherapy for the treatment of lymphoma, confirmed from aspiration and biopsy of an enlarged lymph node, and the mass was seen to decrease in size during follow-up studies (Fig. 5). Although the masses in both ferrets had similar ultrasound characteristics, the renal mass in the second ferret was diagnosed as a spindle cell sarcoma. Additionally that mass had been identified sonographically 1 year prior to the diagnosis of lymphoma, was progressively increasing in size, and did not decrease in size following administration of chemotherapy for the treatment of lymphoma. Concurrent sonographic changes in both ferrets included lymphadenopathy and peritoneal effusion.

A large lobular retroperitoneal mass was present in one ferret. The mass was on midline, extending into the right and left sides of the retroperitoneal space, laterally displacing the right kidney. The left kidney was not visualized radiographically. In the right cranial retroperitoneal space, cranial to the right kidney, there was a cluster of heterogeneous mineral opacities in an adjacent second, smaller

mass. Sonographically the large retroperitoneal mass was heterogeneous, hypoechoic with patchy hyperechoic regions, and laterally displaced both kidneys. The smaller mineralized mass was confirmed to be an enlarged right adrenal gland sonographically. At necropsy, the retroperitoneal mass was confirmed to be lymphoma; however, a specific tissue of origin was not determined. As a normal left adrenal gland could not be identified sonographically or at postmortem, an adrenal origin for this mass was considered most likely, although adrenal tissue was not identified histopathologically within the mass. Alternatively the mass may have arisen from a retroperitoneal lymph node or retroperitoneal adnexa.

Concurrent abdominal imaging findings considered incidental to the diagnosed lymphoma included renal cysts (8), cystic lymph nodes (7), adrenomegaly in ferrets with diagnosed adrenal disease (5), and pancreatic nodules in ferrets diagnosed with insulinoma (2).

On thoracic radiographs pleural fissure lines, consistent with a small volume of pleural effusion, were present in 3/12 ferrets. Pericardial and pleural effusions were noticed during abdominal ultrasonography in one ferret. Possible sternal (2) and tracheobronchial lymphadenopathy (1) were seen radiographically. In one ferret, sternal and cranial mediastinal lymphadenopathy were detected with CT. An interstitial pulmonary pattern was present in two ferrets, but was potentially attributable to the radiographic projections being relatively expiratory.

Aggressive osseous lesions were detected radiographically in three ferrets. The one ferret with a history of lameness had a soft-tissue mass involving the entire right femur with marked, multifocal areas of geographic to moth-eaten, expansile lysis throughout. Smooth to mildly irregular periosteal reaction was present along the femoral diaphysis and greater trochanter. The adjacent acetabulum and ileum were questionably involved based on the radiographs. Sonographically the soft-tissue components of the mass were homogeneously hypoechoic. Cortical irregularities and disruption, consistent with lysis, were also present. Histopathology of the mass following limb amputation was consistent with plasmablastic lymphoma. This ferret was previously described.[8]

Vertebral lysis was apparent radiographically in two of the three ferrets with T3-L3 myelopathy. In one of these two ferrets, there was geographic lysis of L1 involving the majority of the vertebral body and a pathologic fracture of the cranial end plate (Fig. 6). Other radiographic changes present in this ferret included splenomegaly and decreased abdominal serosal detail likely due to poor body condition. On ultrasound, peritoneal effusion, splenomegaly with splenic nodules, and lymphadenopathy were detected. At necropsy, intramedullary lymphoma was found in the L1 vertebra with epidural extension of the tumor. Lymphoma was also found affecting the spleen, liver, pancreas, and

FIG. 6. Right lateral radiograph cropped and centered on L1. At L1 there is geographic lysis, including cortical thinning or loss, of the cranial two-thirds of the vertebral body and the cranial aspect of the pedicles (arrows). The cranial end plate of L1 has a concave indentation, presumptively secondary to a pathologic fracture (arrow head).

mesenteric lymph nodes. In the second ferret with vertebral lysis, there was geographic lysis of the cranial two-thirds of the body and pedicles of T14. There was also possible lysis of the cranial body and pedicles of L4. The dorsal half of the left 9th rib was lytic and no longer visible. Associated with this rib, there was a large, ill-defined, soft-tissue mass, which extended into the thoracic cavity. The adjacent ribs and vertebra were not appreciably involved. Additional radiographic findings in this ferret included splenomegaly, hepatomegaly, and abdominal masses consistent with enlarged lymph nodes. With CT, expansile lysis of the left T14 vertebral body and pedicle was seen associated with a hyperattenuating (to muscle), strongly enhancing mass (Fig. 7). The mass occupied the ventral two-thirds of the spinal canal and resulted in severe spinal cord compression. A possible pathologic fracture was present in the cranial endplate. At L4, there was lysis of the left pedicle and body associated with a mildly compressive, hyperattenuating, contrast-enhancing mass. An additional, similar mass lesion was seen at T4, with lysis of the midvertebral body and mild spinal cord compression. The rib mass was isoattenuating (to muscle), heterogeneous, mildly enhancing, and resulted in severe, expansile lysis. Cytology of the rib mass obtained by ultrasound-guided fine-needle aspiration was diagnostic for lymphoma; cytological assessment of the other lesions was not performed in this ferret.

One ferret with T3-L2 myelopathy did not have gross skeletal pathology. Radiographic changes included splenomegaly and poor, mottled serosal detail. Sonographically, a mild peritoneal effusion was present, and the spleen was considered within incidental variation. An MRI of the lumbar spine revealed an ill-defined area of suspect intramedullary T2w hyperintensity within the spinal cord at the level of L3. Differential diagnoses for this lesion considered at the time included an artifact, prior infarct, gliosis,

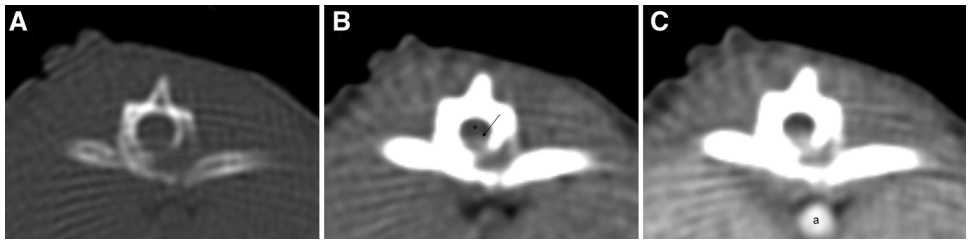

FIG. 7. Transverse, cropped, computed tomography (CT) images of T14 at the midbody (A) precontrast displayed in a bone window (WW 2000, WL 300), (B) precontrast displayed in a soft-tissue window (WW 400, WL 40), and (C) postcontrast displayed in a soft-tissue window. In the left half of the vertebral body and extending dorsally into the pedicle, there is geographic lysis and cortical disruption. These regions are wider when compared to the contralateral aspect of the vertebra, consistent with expansile lysis. On the precontrast image (B) hyperattenuating tissue can be seen in the lytic regions and extending into the ventral spinal canal (arrow) resulting in dorsal displacement and compression of the spinal cord (*). This tissue is heterogeneously enhanced postcontrast (C). There is a streaking artifact on the images, consistent with Poisson noise; a, aorta.

edema, myelitis, neoplasia, and hydromyelia. At the postmortem examination performed 5 months after the MRI, lymphoma was detected in the brain, meninges, choroid plexus, spinal cord, and extracapsular accessory adrenal tissue. Additionally there was multifocal spinal cord malacia and hemorrhage. The lesions in the spinal cord were identified in histopathologic samples obtained at intervals from the cervical spine at C1 through to the lumbar spine at L5, including at the level of L3. Specific correlation between the suspect MRI lesion and histopathologic findings was not performed. Splenic changes were consistent with congestion and extramedullary hematopoiesis.

Discussion

Multicentric lymphoma was the most common presentation in this study. This is consistent with prior reports in which multicentric lymphoma is the most common presentation in ferrets older than 3 years of age.[1,5,6,12] The most common imaging findings in this study were intra-abdominal lymphadenopathy and splenomegaly with mild-to-moderate peritoneal effusion. Lymphadenopathy consisted of multiple enlarged, predominantly intra-abdominal lymph nodes, particularly including the mesenteric lymph node. Only one ferret had peripheral lymphadenopathy, consisting of enlargement of the inguinal and popliteal lymph nodes, in addition to abdominal lymphadenopathy. Lymph nodes greater than 6.2 mm thick sonographically were generally appreciable radiographically as round to oblong, soft-tissue nodules or masses in their respective locations. Of the three ferrets in which sonographically detected lymphadenopathy was not appreciable radiographically, only one had a lymph node thickness greater than 6.2 mm. That ferret also had a large, retroperitoneal mass that likely accounted for a lack of visualization of the enlarged mesenteric lymph node due to silhouetting and displacement. Previous studies in normal ferrets using ultrasound have reported the normal thickness of mesenteric lymph nodes as 5.3 ± 1.39 mm and 7.6 ± 2.0 mm.[13,14] Given that some radiographically visible lymph nodes measured as small as 6.2 mm (which is within the reported normal ranges for mesenteric lymph nodes) it is possible that normal lymph nodes may be radiographically appreciable. In the authors' experiences, however, visualization of normal, small abdominal lymph nodes on radiographs of ferrets is uncommon. Normal abdominal lymph nodes are not radiographically distinguishable in dogs and cats.[15,16] Although some lymph nodes in this study that were considered abnormal measured within the reported normal ranges, there were other changes to those nodes to suggest pathology, such as hypoechogenicity. In dogs and cats, sonographic changes that have been associated with malignancy include an increase in maximal short and long axis diameter (enlarged), an increase in short-to-long axis length ratio (more rounded appearance), hypoechogenicity, hyperechoic perinodal fat with an irregular nodal contour, and heterogeneity.[17–19]

Similar to previous reports, the spleen was the most common extranodal site of neoplastic infiltration with lymphoma in the current study.[5] In a prior study splenomegaly was attributable to neoplastic infiltration in 67% of ferrets with lymphoma and extramedullary hematopoiesis in 33%.[5] In general, splenomegaly secondary to extramedullary hematopoiesis is common in ferrets.[2] To the authors' knowledge, there is no reference for normal splenic size in ferrets using ultrasound. Grossly the normal spleen has been reported to measure 5.1 cm in length, 1.8 cm in width, and 0.8 cm thick.[20] Given that these are gross measurements, however, they were likely obtained postmortem. Splenic size is variable and decreases postmortem, so these measurements may not be translatable to antemortem studies with sonographic measurements.[21] The smallest splenic thickness in this study was 0.8 cm; using the gross measurement guidelines all spleens in this study would be considered enlarged. The degree of splenomegaly was therefore subjectively characterized as within incidental variation and larger than expected for "incidental splenomegaly" based on the authors' experiences. Of the seven ferrets in which splenic cytology was available, lymphoma was confirmed

in the four ferrets in which the spleen was considered abnormal and cytology was performed. Of the three ferrets spleens in which cytology was performed and the spleen was considered within incidental variation, lymphoma was identified in one, and extramedullary hematopoiesis was confirmed in the other two.

Potential differential diagnoses for multicentric lymphadenopathy with splenomegaly in ferrets include reactive lymphadenopathy secondary to gastrointestinal disease with splenic extramedullary hematopoiesis, systemic mycobacteriosis, granulomatous inflammatory syndrome, and Aleutian Disease.[1,22–25] With systemic mycobacteriosis, ferrets can have other lymph nodes affected in addition to the abdominal lymph nodes, with the retropharyngeal lymph nodes being affected as commonly as the mesenteric lymph nodes.[25] As with lymphoma, clinical signs of mycobacteriosis in the ferret depend on the organs that are affected and can include lethargy, anorexia, vomiting, and diarrhea; but as with other infectious diseases, changes in white blood cell counts can be seen. Mycobacteriosis can be diagnosed on cytology and biopsy of the affected lymph node or organ.[25] Granulomatous inflammatory syndrome is a newly recognized systemic disease associated with coronavirus that causes inflammation in the spleen and lymph nodes.[23] This syndrome results in a severe granulomatous disease that can affect the gastrointestinal tract, mesenteric lymph nodes, liver, and spleen. Unlike lymphoma, it is usually seen in younger ferrets, but like lymphoma, clinical signs are nonspecific and depend on the organ that is affected. Patients with this syndrome usually have polyclonal gammopathy that can also be seen with Aleutian's disease virus and lymphoma. Definitive diagnosis requires cytology or biopsy of the affected organs.[23] Aleutian's Disease is a parvovirus that can cause lymphadenopathy and splenomegaly. As with lymphoma and granulomatous inflammatory syndrome, Aleutian's Disease can cause a polyclonal gammopathy. Ferrets with this virus usually present with generalized signs of illness (lethargy, weight loss) as well as neurologic signs such as paresis or tremors.[24] Aspirates and biopsy samples of lymph nodes and the spleen can be difficult to interpret as the disease causes lymphoplasmacytic inflammation that can be easily confused with other diseases such as small cell lymphoma and Epizootic Catarrhal Enteritis.[24]

In the one ferret with colonic lymphoma, there were minimal imaging findings including poor abdominal serosal detail and mild peritoneal effusion. At postmortem, lymphoma with mucosal erosions was detected in the colon. Segmental lymphoplasmatic enteritis was identified in the small intestines. This ferret presented cachexic, hypotensive, anemic, had melena, and died within 24 h of presentation. Given that melena is referable to upper gastrointestinal bleeding, the clinical findings in this ferret could have been attributable to both *Helicobacter mustelidae* gastritis and lymphoma. It is also possible that lymphoma was present in other portions of the gastrointestinal tract, but was not detected postmortem.

After the spleen, the next most common extranodal sites of neoplastic involvement with lymphoma in ferrets have been reported to be the liver, kidneys, and lungs.[5] In this study, two ferrets had confirmed hepatic infiltration—one of which had mild hepatomegaly on ultrasound (subjectively normal on radiographs) and the other of which had no reported hepatic abnormalities. Hepatic lipidosis, identified in four ferrets, was not associated with radiographic or sonographic changes and may have been due to inappetence.[26] Given these findings, ultrasound does not appear to be sensitive for the detection of hepatic lymphoma in ferrets. Sensitivity of ultrasound for hepatic lymphoma has also been reported to be low in dogs, cats, and humans.[27,28] One of two ferrets with renal masses had probable renal lymphoma based on the response to treatment. The second renal mass, a confirmed renal sarcoma, was not sonographically differentiable from the presumptive renal lymphoma. Pulmonary involvement was not identified in this study. The small number of individuals in this study precludes extensive comparisons of the affected organ distribution to prior studies.

The most common thoracic finding in this study was mild pleural effusion, which was present in four ferrets. There were no ferrets with a mediastinal mass in this study. Mediastinal involvement, in general, is more prevalent in ferrets less than 3 years of age, and has been reported to be the more common presentation of lymphoma in that age group with or without concurrent multicentric involvement.[1–3] Ferrets with mediastinal lymphoma may present for tachypnea or dyspnea secondary to the space-occupying effect of a large mediastinal mass, as well as concurrent pleural effusion. No ferrets in this study were less than 3 years old, which may have accounted for the lack of mediastinal involvement in this cohort. Additionally, although this institution also provides primary care to nontraditional small mammal species, it is also a tertiary care facility and the population of ferret patients may not have been representative of the general domestic ferret population. There may have been a selection bias for ferrets with more insidious signs, which tend to occur in ferrets greater than 3 years of age, as opposed to younger ferrets, which may have a more acute and more rapidly progressive presentation.

Aggressive osseous lesions were present in three ferrets with skeletal lymphoma involvement. To the authors' knowledge, only three other ferrets with osseous involvement have been described previously.[2,9] In those ferrets, lytic lesions were present in the tibia, in the lumbar spine, and in the lumbosacral spine.[2,9] Based on those ferrets and the ferrets in this study, it is possible that the lumbar spine is a predilection site for vertebral lymphoma; however, this remains speculative. An alternate possibility is that lysis

may be relatively easier to detect in the lumbar spine where there is less superimposition of structures over the vertebrae, compared to the thoracic vertebrae where the ribs proximally are superimposed on the vertebrae. In humans with primary bone lymphoma, three radiographs patterns are described: the lytic-destructive pattern, which is predominantly lytic with or without a lamellated or interrupted periosteal reaction or cortical lysis; the blastic-sclerotic pattern in which there are mixed lytic and sclerotic regions; and "near-normal" findings in which there are only subtle radiographic changes and additional imaging (scintigraphic bone scans or MRI) is required.[29] Osseous lesions seen in the ferrets of this study and the prior reports are similar to the lytic-destructive pattern, and had cortical disruption. This is also the pattern most typically seen in canines and felines with osseous involvement from lymphoma or other round cell neoplasms.

Diffuse central nervous system infiltration with lymphoma was present in one ferret. As lymphoma outside of the central nervous system was only detected in accessory adrenal tissues, this ferret presumably had a primary central nervous system lymphoma. Primary central nervous system lymphoma in dogs and cats has not been reported to have an extraparenchymal vs. an intraparenchymal predilection.[30] In humans, lesions with primary central nervous system lymphoma are most frequently intraparenchymal, and metastatic central nervous system lymphoma is more frequently extraparenchymal.[30,31] In this ferret, the meninges and choroid plexus were involved in addition to the brain and spinal cord. Protracted clinical signs in that ferret consisted of variable paraparesis and lumbar pain over 8 months from the start of clinical signs to the final diagnosis of lymphoma at necropsy. Gradual progression of signs and the protracted clinical signs suggests a relatively slow-growing process. Prednisone, administered for palliative treatment, was started approximately 3 months after the initial clinical signs. Radiographs and ultrasound, performed prior to starting prednisone, had minimal, nonspecific findings. Magnetic resonance imaging, performed 1 month after initiation of the prednisone regimen and 5 months prior to the diagnosis of lymphoma, was inconclusive. Administration of prednisone prior to the MRI may have resulted in partial regression of lymphoma, therefore making it more difficult to identify; however, the ferret did not demonstrate improvement of the clinical signs so whether prednisone affected detection of neoplastic infiltration or not is speculative. Additionally the MRI was limited in that only T2w images were obtained. Perhaps if additional sequences were performed, particularly T1w postcontrast images, or if a follow-up MRI was performed at a later date, meningeal or parenchymal abnormalities may have been detected. Also because the necropsy was performed 5 months following MRI, it is likely that the extent of the lesions seen postmortem had progressed compared to at the time of imaging. Magnetic resonance imaging lesions in dogs and cats with primary central nervous system lymphoma (compared to white matter) have been reported to be predominantly T2w hyperintense with indistinct margins, T1w hypointense, contrast enhancing, had perilesional hyperintensity on FLAIR consistent with perilesional edema, and had a mass effect.[30] In humans, lesions have similar signal characteristics (compared to white matter) being T2w hyperintense, T1w iso- to hypointense, and contrast enhancing.[30,31] These findings are considered nonspecific in dogs, cats, and humans, and lesions may not be detected with MRI at the onset of clinical signs.[30,31]

Two ferrets had no clinical signs referable to lymphoma. In one ferret, the owner palpated a markedly enlarged abdominal lymph node. Radiographic and sonographic findings consisted of multicentric lymphadenopathy, peritoneal effusion, a renal mass, a hyperechoic liver, and "incidental splenomegaly." In the other ferret, progressive lymphocytosis was detected during routine treatment and monitoring of adrenocortical disease. Lymphoma was identified in the peritoneal effusion of that ferret. Additional sonographic findings included a multicentric lymphadenopathy, splenomegaly with splenic nodules, a cystic hepatic mass, and a renal mass (sarcoma).

Adrenal disease was a common comorbidity seen with lymphoma, as found in other studies.[32] This is likely because adrenal disease is common in older ferrets in general.[1,4,33] Other relatively common comorbidities found in this study were cardiovascular disease and cutaneous mast cell tumors, both of which also commonly occur in older ferrets.[1,33] One ferret had a history of granulomatous lymphadenitis suspected to be secondary to mycobacteriosis.

Although this study describes the imaging findings in a small number of ferrets with lymphoma, it provides an important source of information for practicing clinicians. The small number of ferrets able to be included during the time frame of the study likely reflects that imaging is not performed in every ferret with suspected or confirmed lymphoma, and that a definitive diagnosis was not always attained prior to treatment in individuals with suggestive clinical and imaging findings. Ultrasound-guided aspirates of lymph nodes, spleens, and aggressive osseous lesions performed in ferrets of this study were each diagnostic for or strongly suggestive of lymphoma. Although aspirates are often the initial tissue sampling procedure, previous reports have cautioned the use of lymph node aspirates in the diagnosis of lymphoma as inflammatory and reactive changes may be misinterpreted as lymphoma.[1,3] This is particularly true of the gastric lymph node in ferrets with gastrointestinal signs. A false positive diagnosis of lymphoma is considered not likely to have occurred in the ferrets included for in this study. Lack of a definitive diagnosis (i.e., false negative results) from aspirate samples likely resulted in exclusion of some individuals from this study. Analysis of the frequency

of misdiagnosis and nonconfirmatory aspirate samples in patients with lymphoma was not performed. This study was also limited in that histopathology was not performed on all organs in each individual, and therefore, whether or not the changes seen were each attributable to lymphoma cannot be confirmed. Additionally, because ultrasound findings were based on the reports and images obtained; some structures were unable to be reassessed. This is particularly the case in which multiple lymph nodes were affected. Images of each lymph node may not have been attained, the imaging report may not have been complete in describing which nodes were affected, and measurement performed retrospectively on the available static images may not have reflected the actual maximal nodal thickness in that individual.

In conclusion, findings from the current study indicated that imaging characteristics of lymphoma in ferrets are similar to those previously reported for dogs, cats, and humans. Lymphoma may most commonly be multicentric in ferrets. Imaging findings frequently included intra-abdominal lymphadenopathy, splenomegaly, and peritoneal effusion. Lymphadenopathy and mass lesions were typically hypoechoic on ultrasound. Osseous lesions, when present, were predominantly lytic. Lack of imaging abnormalities did not preclude the diagnosis of lymphoma.

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