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CASE REPORT
Lymphangiosarcoma in two cats

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Lymphangiosarcoma is a malignant neoplasm of the lymphatic endothelium that is rare in cats. This report describes two cases of feline lymphangiosarcoma that originated in the distal limb, causing intractable lymphoedema and serosanguineous discharge with ecchymoses in local and distant sites. In association with the neoplasia, one cat had cortical bone lysis of multiple metacarpal bones of the affected limb and the other had severe immune-mediated haemolytic anaemia (IMHA). The disease in both cases affected young cats and progressed rapidly. Persistent distal limb lymphoedema with serosanguineous discharge is suggestive of lymphangiosarcoma especially when local or distal ecchymoses are evident.

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Case 1

A 2-year-old spayed female domestic longhair cat (6.2 kg) was referred to Murdoch University Veterinary Hospital (MUVH) with a 2-week history of acute-onset, non-progressive swelling and haemorrhagic discharge of the left pes. There had been little response to antimicrobial therapy prescribed by the referring veterinarian. The cat was pyrexic (39.6°C) with pale mucous membranes, a grade II/VI murmur over the left cardiac apex, moderate enlargement of both popliteal lymph nodes and mild enlargement of both mandibular lymph nodes. Marked pitting oedema was present in the left hind limb between the pes and stifle with a focal swelling around the fourth digit. Multiple raised, erythematous plaques (2–4 mm diameter) were present in the plantar interdigital skin surrounding the fourth digit, with a haemorrhagic discharge oozing from these lesions (Fig 1). Multiple petechial and ecchymotic haemorrhages were also present on the medial and caudal aspects of the left thigh region.

Haematology revealed a severe anaemia (packed cell volume (PCV) 0.12 l/l; normal 0.28–0.45 l/l) with a marked regenerative response (reticulocyte percentage 9.7%). Serum total protein was normal (63.5 g/l, normal 54–78 g/l), as was the platelet count (209×10^9 cells/l; normal $156–626 \times 10^9$ cells/l). Spherocytes were suspected but not clearly identified. Neither autoagglutination (saline autoagglutination test) nor cytological evidence of *Mycoplasma haemofelis* was detected. Serum biochemistry and urinalysis were normal and serological tests for feline immunodeficiency virus, feline leukaemia virus and feline coronavirus were negative. Prothrombin time was rapid (6.2 s; normal 8.4–10.8 s) and activated partial thromboplastin time was mildly prolonged (32.1 s; normal <30.2 s). Buccal mucosal bleeding time was normal (<2 min). A significant coagulopathy was excluded and, retrospectively, the results were consistent with a diagnosis of haemolytic anaemia; at the time, anaemia was incorrectly attributed to haemorrhage from the left pes. A pressure bandage was applied to the left hind limb and the cat received a transfusion of whole cross-matched blood (60 ml).

Radiographs of the left pes revealed moderate soft tissue swelling around the fourth digit but no bony abnormalities. Thoracic radiographs were unremarkable. Multiple skin biopsies were taken from the lesions of the digits and medial thigh and submitted for histopathology and

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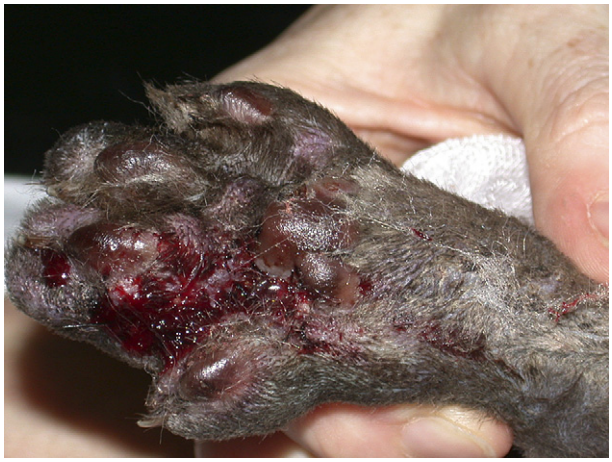

Fig 1. Plantar aspect of left pes of case 1. There is moderate swelling of the digits with a haemorrhagic discharge oozing from around the fourth digit.

microbiology. Cytological aspirates from the left popliteal lymph node were consistent with an oedematous, reactive lymph node.

Whilst awaiting the results, the cat was treated with ciprofloxacin (for broad spectrum cover against Gram-positive and Gram-negative organisms including mycobacteria, which may have been responsible for draining sinus tract lesions; 250 mg q 12 h PO), doxycycline (specifically for the possibility of mycobacterial lesions; 100 mg q 12 h PO) and pressure bandaging. Five days later, the cat presented again with weakness. The fourth digit of the left pes had increased in size and erythematous plaques on the medial thigh had increased in number (Fig 2). The cat's anaemia had worsened (PCV 0.04 l/l; protein 70 g/l) and was attributed to further haemolysis. Another transfusion of whole, cross-matched blood (40 ml) was administered and the PCV post-transfusion was 0.14 l/l.

Microbiological cultures and histopathology (haematoxylin and eosin, periodic acid-Schiff, Gram and Ziehl–Neelsen stains) of the skin biopsies did not reveal bacteria or fungi. A preliminary histopathological diagnosis of granulomatous lymphangitis with areas of mixed skin inflammation was made pending the interpretation of further stains.

There was rapid progression of the lesions, and an underlying neoplastic process was suspected. Due to concerns that the limb lesion was a precipitating factor in the haemolytic anaemia and that haemorrhage from the lesion would exacerbate the anaemia, a decision was made to amputate the fourth digit to obtain a representative excisional biopsy. Abdominal ultrasonography prior to surgery was unremarkable. The fourth digit of the left pes was amputated; histopathology revealed multiple dilated lymphatics, many containing spindle-shaped cells that stained positively for factor VIII (Fig 3). Plump aggregates of abnormal cells were present within the lymphatic channels extending to the surgical margins (Fig 4). The histopathological diagnosis was lymphangiosarcoma. Review of the previously obtained skin biopsies confirmed the same lesions, hence the preliminary histopathological diagnosis of granulomatous lymphangitis was considered a mis-diagnosis. Ciprofloxacin

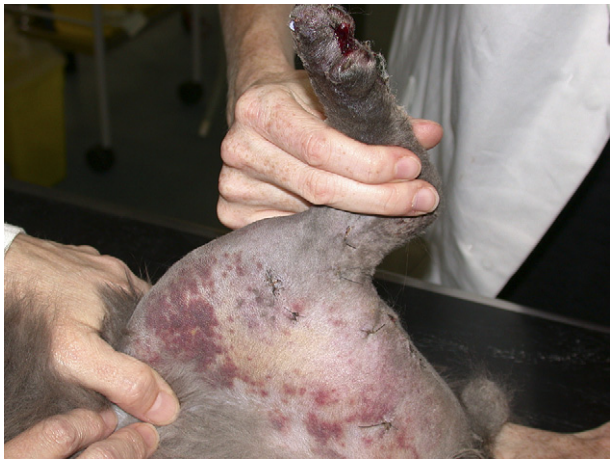

Fig 2. Medial aspect of left hind limb after skin biopsies in case 1. Multiple petechial haemorrhages are present and there is moderate oedema of the limb. Haemorrhagic discharge from the digits is evident.

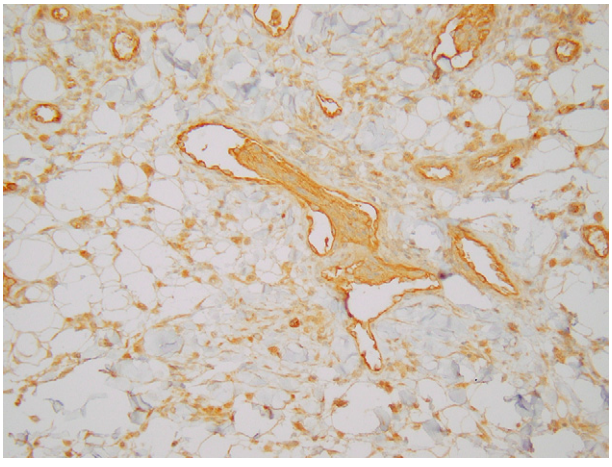

Fig 3. Skin, dermis, case 1. Immunohistochemistry for factor VIII-related antigen (brown reaction product) confirms the endothelial origin of the cells lining the vessels and those forming the intraluminal projections. Haematoxylin and eosin, ×20 objective.

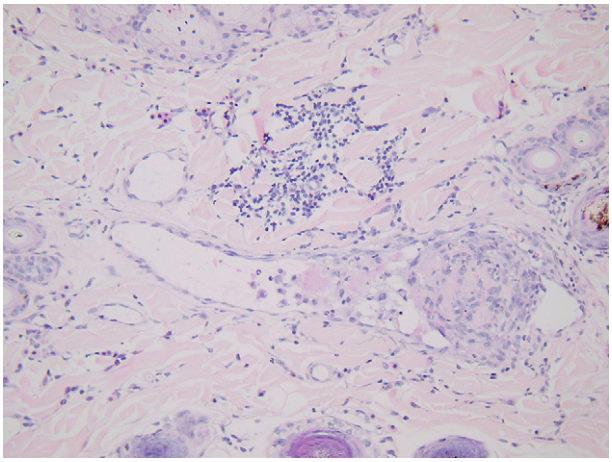

Fig 4. Skin, dermis, case 1. Lymphatic-like vessels lined by flattened endothelial cells with occasional intraluminal proliferative masses. Haematoxylin and eosin, ×20 objective.

and doxycycline treatment continued and prednisolone (10 mg q 12 h PO) was added to the therapy. One week later, the cat had very pale mucous membranes and new haemorrhagic plaques were detected on the medial thigh and ventral abdomen. Due to the poor prognosis, the owner elected to euthanase the cat. Necropsy was not performed.

Case 2

A 6-year-old, castrated male domestic shorthair cat presented to MUVH for mild lameness and swelling of the pads of the left manus of 3 weeks' duration. Treatment for cellulitis by the referring veterinarian (unspecified antibiotic and anti-inflammatory therapy) did not improve the swelling and a serosanginous discharge developed from between the pads of manus. Radiographs of the left manus made by the referring veterinarian at the time of initial presentation were assessed as normal.

On presentation to MUVH, the cat was in slightly thin body condition (5.01 kg), pyrexic (39.3°C) and tachypnoeic (48 breaths per minute). The left manus was diffusely swollen, erythematous and painful, and there was a serosanguineous discharge draining from a small skin laceration on the palmar aspect of the fourth digit. A grade III/VI systolic heart murmur was detected. Packed cell volume and total plasma protein were normal (0.32 l/l and 60 g/l, respectively).

Radiographs of the left forelimb revealed a diffuse thickening of the soft tissues of the distal limb. In the diaphysis of the third metacarpal bone, subtle circumferential cortical lysis created a very mild scalloped appearance to the periosteal surface of the bone (Fig 5). No periosteal new bone or medullary lysis was present. Ultrasonography of the swollen soft tissues did not detect an aetiology. Fine needle aspirates of the swollen manus were non-specific and did not provide a definitive diagnosis. Primary bacterial culture of the discharge fluid was negative; *Enterobacter* species was cultured from an enrichment broth and presumed to be a contaminant. Thoracic radiography and limited echocardiography (cardiac function assessment) were normal. A cause of the grade III systolic murmur was not detected. Infection and cellulitis of the manus were considered less likely given the cytology and culture results. Primary or secondary lymphoedema was diagnosed and the cat was treated with procaine penicillin (to target anaerobes; 6.25 mg q 12 h subcutaneously), ciprofloxacin (for broad spectrum cover against Gram-positive and Gram-negative organisms including mycobacteria, which may have been

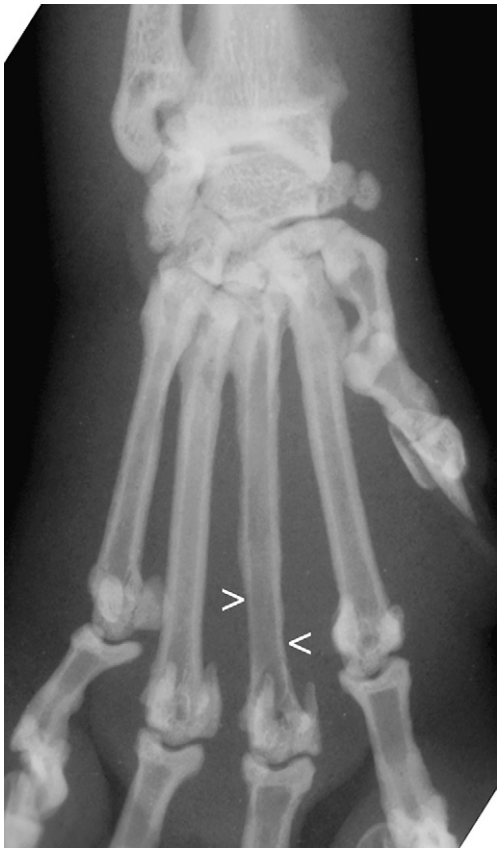

Fig 5. Radiograph of the left manus of case 2 at presentation. Along the length of the diaphysis of the third metacarpal bone, there is a mild, scalloped appearance to the cortex (white arrowheads).

responsible for draining sinus tract lesions, 62.5 mg q 12 h PO) and rutin (250 mg q 12 h PO).

Two days later, the swelling in the manus had decreased slightly and the lameness had improved but the serosanguineous discharge persisted. The pyrexia had resolved (37.8°C) and the cat was discharged after the owner declined further investigation. The cat presented 5 days later with inappetence, persistent lameness and limb swelling and was treated with oral prednisolone (40 mg for the first day PO, followed by 20 mg q12 h PO). The cat re-presented after 24 h with tachypnoea (42 breaths per minute) and inappetence. Ultrasonographic examination of the thorax did not reveal pleural effusion and the tachypnoea resolved over 24 h with cage rest. The swelling and discharge of the left manus persisted.

Repeat radiographic examination of the thorax was normal − there was no evidence of pulmonic metastatic disease or pleural effusion. Limb amputation was performed at the referring veterinary hospital, and the limb submitted to MUVH for pathology. Radiographs of the amputated limb (approximately 3 weeks after the initial radiographic study) revealed a progression of the scalloped cortical lysis of the metacarpal bones, involving the diaphysis of the second, third and fifth metacarpal bones (Fig 6).

Microbiological culture from swabs of the dissected manus grew a mixture of *Streptococcus* species, coryneform bacteria and *Staphylococcus* species, presumed to be contaminants. Histopathological examination revealed an extensive dermal and subcutaneous proliferation of neoplastic, spindle-shaped mesenchymal tissue that dissected around dermal collagen, vessels and other anatomical structures, with a moderately high mitotic rate. The cells stained positive with vimentin, variably positive for factor VIII and negative with cytokeratin. A diagnosis of lymphangiosarcoma was made. No comment about the surgical margins was recorded.

The cat was palliated at home with chemotherapeutic doses of prednisolone. Fifteen days later, ecchymotic haemorrhages were noted in the oral cavity and at the commissures of the oral labia. Ventral oedema and ecchymoses over the thorax were also evident. The cat was euthanased. Necropsy and histopathological examination confirmed the original diagnosis of lymphangiosarcoma and identified its spread to involve the soft tissues of the neck, thorax and parietal pleura. Thrombosis of the distal left jugular vein, extensive cutaneous and subcutaneous haemorrhage and oedema in the skin over the left thorax and ventral neck, and a bilateral serosanguineous chylous pleural effusion were all associated with the infiltration of the lymphangiosarcoma. Mild concentric left ventricular cardiac hypertrophy of unknown significance and aetiology was also identified at necropsy.

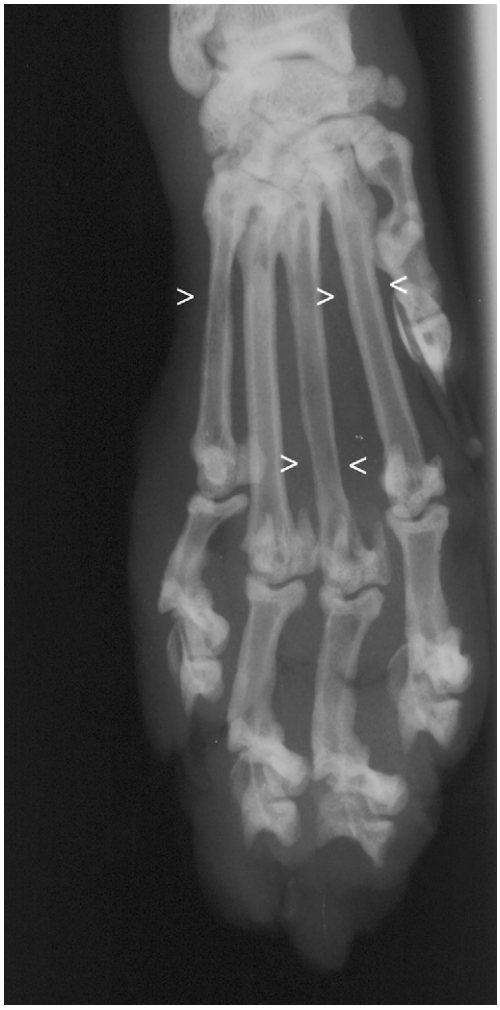

Fig 6. Dorsopalmar view of the left manus, case 2, 3 weeks after the radiographic examination shown in Fig 3. There is progression of the scalloped cortical lysis, affecting metacarpal bones 2, 3 and 5 (white arrowheads). The fourth metacarpal bone is spared.

Discussion

Lymphangiosarcoma is a rare, malignant neoplasm of the lymphatic endothelium, which can occur at any site. There are relatively few reports in the cat (Patnaik and Liu 1977, Walton and Scott 1983, Walsh and Abbott 1984, Swayne et al 1989, Stobie and Carpenter 1993, Gores et al 1994, Hinrichs et al 1999, Galeotti et al 2004).

In humans, chronic lymphoedema can cause lymphangiosarcoma. Stewart–Treves syndrome, an aggressive form of lymphangiosarcoma, can develop in post-mastectomy patients (Chung et al 2000) and others with primary or secondary lymphoedema. In domestic species, this is extremely rare with only one report of primary lymphoedema in a dog leading to the induction of lymphangiosarcoma (Webb et al 2004).

The most frequent reports of feline lymphangiosarcoma describe poorly defined masses or subcutaneous thickening and oedema of the skin of the caudoventral abdomen (Walsh and Abbott 1984, Carpenter et al 1987, Swayne et al 1989, Hinrichs et al 1999, Galeotti et al 2004). Draining tracts with haemorrhagic to serosanguineous fluid have been associated with focal, erythematous, hyperpigmented macules in the skin of the abdomen (Walsh and Abbott 1984, Swayne et al 1989, Galeotti et al 2004). Cases of chylous pleural and peritoneal effusion due to lymphangiosarcoma in the cranial mediastinum and mesentery, respectively, have also been reported (Swayne et al 1989, Stobie and Carpenter 1993, Hinrichs et al 1999).

An extensive literature search of computerised databases revealed only one case of lymphangiosarcoma originating in the distal limb in a cat; two case reports were written about this patient (Walton and Scott 1983, Walsh and Abbott 1984). Five additional, unpublished cases describing lower limb involvement were described in a textbook (Carpenter et al 1987), bringing the total number of cases involving a distal limb to six. In the published report (Walsh and Abbott 1984), a 6-year-old spayed female domestic shorthair cat presented with a 1-month history of a discharging wound between the digits of the left manus. Radiography of the left forelimb was unremarkable; the limb was amputated and histopathology was not performed. Ten months later the cat developed draining tracts, multifocal ecchymoses and petechiae on the ventral thorax, thrombocytopenia and gastrointestinal haemorrhage. Lymphangiosarcoma was diagnosed after post-mortem and histopathological examination.

The two cats in the current case series presented with distal limb lymphoedema and persistent serosanguineous discharge from a digit. The lymphoedema progressed proximally to involve the stifle in one case and the elbow in the other. In the terminal phase of the disease, both cats developed extensive bruising and oedema on the ventral thorax and abdomen indicating widespread metastatic disease. The second cat developed chylous pleural effusion by the time of euthanasia; despite normal thoracic radiographs 16 days prior.

Case 2 had radiographically detected bony changes in the affected limb. To the authors' knowledge, this is the first report of bony changes secondary to lymphangiosarcoma. Radiography initially showed diffuse thickening of the soft tissues of the distal limb due to lymphoedema. Subtle, circumferential, cortical lysis gave the periosteal surface a scalloped appearance; the lesion initially affected one metacarpal bone but progressed to involve three. Periosteal new bone reaction and medullary cavity lysis were not present, and the fourth metacarpal was apparently spared. Unfortunately, histopathology was not performed on the bone lesions. We speculate that the lysis was secondary to the effects of increased pressure on the periosteal surface of the bones from chronic lymphoedema, as chronic pressure is known to induce bone resorption and remodelling (Park et al 1996).

Both cats in this series presented with petechiae and ecchymoses, indicative of defective primary haemostasis (Brooks and Catalfamo 2005). Coagulation tests performed in case 1 were unremarkable and platelet count and buccal mucosal bleeding time were normal, indicating a local vascular abnormality (Brooks and Catalfamo 2005). The cause of this primary haemostatic defect is difficult to ascertain, but it appears to be a feature in all species that are affected by lymphangiosarcoma (Ruggles et al 1992, Hinrichs et al 1999,Chung et al 2000, Sanchez et al 2002, Williams 2005).

Case 1 had a severe, regenerative, haemolytic anaemia. Initially the cause of the anaemia was attributed to haemorrhage from the foot lesion; however, total serum protein concentration was consistently normal indicating that the anaemia was, in fact, haemolytic. Anaemia does not appear to be a consistent feature of the reported cases of feline lymphangiosarcoma (Patnaik and Liu 1977, Walton and Scott 1983, Swayne et al 1989, Stobie and Carpenter 1993, Hinrichs et al 1999, Galeotti et al 2004). One previous report of lymphangiosarcoma affecting the ventral abdomen in a 7-year-old Persian cat described a very mildly regenerative anaemia (haematocrit 0.23 l/l); however, the anaemia was not characterised further (Walsh and Abbott 1984).

Haemolytic anaemia may be caused by infectious or non-infectious agents (Cowell 1997). In case 1, infectious causes were considered unlikely. Serological tests for feline immunodeficiency

virus, feline leukaemia virus and feline coronavirus were negative. *Mycoplasma haemofelis* was not detected on smears and although polymerase chain reaction testing was not performed, there was no response to symptomatic treatment. Non-infectious causes of haemolytic anaemia include primary immune-mediated haemolytic anaemia (IMHA), toxic causes, microangiopathy and congenital enzyme abnormalities, with primary IMHA being very rare in the cat (Cowell 1997). Secondary IMHA can occur as a paraneoplastic condition and although the exact incidence is unknown, paraneoplastic IMHA is relatively common in humans and animals (Bergman 2001). We speculate the IMHA in case 1 was most likely secondary to the underlying neoplastic condition. IMHA has not been previously reported in cats with lymphangiosarcoma.

Cytology was not a useful tool for the diagnosis of this disease. Diagnosis of lymphangiosarcoma can be confirmed by biopsy and histopathology. In case 1, the lesion was initially misdiagnosed as granulomatous lymphangitis; this may reflect the subtleties of the neoplastic characteristics in this tumour. Lymphangiosarcoma is characterised by poorly defined proliferation of spindle cells forming vascular clefts or cavernous spaces (Hinrichs et al 1999, Galeotti et al 2004), features present in both cases. The identification of factor VIII-related antigen and vimentin with immunohistochemistry confirmed the cells were of endothelial origin (Fox et al 2005). Cytological atypia, abnormal vessel formation and inappropriate proliferation and behaviour assisted in the differentiation of neoplasia (lymphangiosarcoma and haemangiosarcoma) from normal vascular endothelial cells. The absence of significant amounts of blood within the abnormal vascular channels was used to discriminate between lymphangiosarcoma and haemangiosarcoma in these cases. Recently new markers (lymphatic vessel endothelial receptor-1 (LYVE-1), podoplanin and PROX-1)) have been developed which are capable of distinguishing neoplastic endothelial cells from normal blood and lymphatic endothelium (Galeotti et al 2004). LYVE-1 has been used to successfully diagnose lymphangiosarcoma in cats (Galeotti et al 2004). Use of these newer markers may improve the ability to detect lymphangiosarcoma in cats in the future.

From previously published reports the prognosis with lymphangiosarcoma is extremely poor and both cats in this series had rapid progression of the disease. No signs of metastasis were detected at initial presentation; however, both cats developed signs of disease progression within weeks. No curative treatments are currently available for dogs or humans affected by the condition, with the majority surviving only a few months after diagnosis (Williams 2005). Surgical excision in case 2 did not seem to significantly alter the progression of disease, with euthanasia occurring secondary to extensive spread of the neoplasm within 3 weeks. The previously reported cat with lymphangiosarcoma of the left forelimb lived for 10 months after amputation before widespread metastases led to euthanasia (Walsh and Scott 1984); however, all other reported cases had much shorter survival times. Had amputation been performed more promptly in case 2, survival time may have increased. The benzopyrone drug rutin was used in case 2 with the aim of reducing lymphoedema by promoting proteolysis, stimulating macrophages and enhancing the absorption of protein fragments (Mertens et al 2005). It was not effective.

Lymphangiosarcoma is a highly aggressive malignant neoplasm of the lymphatic endothelium that is rare in cats. Bony lesions and IMHA have not been described in previous cases. Distal limb lymphoedema would appear to be an uncommonly reported manifestation of this disease in the published literature. This case report describes very similar findings to other cases of distal lymphoedema, particularly those of Carpenter et al (1987). Distal limb lymphoedema accompanied by serosanguineous discharge, draining tracts and local or distal ecchymoses is highly suggestive of lymphangiosarcoma. Lymphangiosarcoma should be considered as a differential diagnosis for this spectrum of clinical signs in cats.

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