Appendicular arterial tumor embolization in two cats with pulmonary carcinoma

Patricia Ibarrola, DVM; Alexander J. German, BVSc, PhD; Anneliese J. Stell, BVM&S; Richard Fox, BvetMed; Nuala J. Summerfield, BVM&S, DACVIM; Laura Blackwood, BVMS, PhD

A 13-year-old neutered male Persian cat was referred for evaluation of left forelimb lameness of 72 hours' duration. The cat had a 6-month history of suspected allergic pulmonary disease, which was controlled with prednisolone (1 mg/kg [0.45 mg/lb], PO, q 24 h). Six days prior to referral, the cat had been examined on an emergency basis because of a sudden onset of left hind limb lameness and hind limb ataxia, and the prednisolone dosage had been increased (2.5 mg/kg [1.14 mg/lb], PO, q 12 h). The cat's condition improved slightly, but intermittent lameness and ataxia persisted. Following the onset of left forelimb lameness, the cat was treated with amoxicillin-clavulanate (12.5 mg/kg [5.7 mg/lb], PO, q 12 h) and prednisolone at the same dosage, but there had not been any improvement. Vaccinations were current; the cat had free access to the outdoors.

Abnormalities evident on physical examination included mild dehydration, tachypnea (50 breaths/min) with slight hyperpnea, and a generalized increase in bronchovesicular sounds. No cardiac abnormalities were detected, and there were palpable femoral pulses in both hind limbs. Gait analysis revealed knuckling and weakness of the left forelimb. There were proprioceptive deficits, and the extensor carpi radialis reflex and flexor withdrawal reflex were decreased. Hematologic abnormalities included neutrophilia (14.9 X 10^9 cells/L; reference range, 2.5 to 12.5 X 10^9 cells/L), lymphopenia (1.0 X 10^9 cells/L; reference range, 1.5 to 7.0 X 10^9 cells/L), and thrombocytosis (620 X 10^9/L; reference range, 150 to 400 X 10^9/L). Serum biochemical abnormalities included mild azotemia (urea, 12.4 mmol/L [reference range, 2.5 to 7.5 mmol/L]; creatinine, 125 µmol/L [reference range, 40 to 120 µmol/L]), hypernatremia (166 mEq/L; reference range, 145 to 156 mEq/L), hyperglycemia (8.2 mmol/L; reference range, 3.5 to 6.5 mmol/L), and moderately high alkaline phosphatase (80 U/L; reference range, 0 to 40 U/L) and ala-
nine aminotransferase (229 U/L; reference range, 7 to 50 U/L) activities. Specific gravity of a urine sample was 1.060; results of a urinalysis were otherwise unremarkable.

Blood flow in the brachial arteries was assessed with a Doppler ultrasonic flow detector. No blood flow was detected in the left brachial artery, whereas blood flow in the right brachial artery was easily documented. Results of survey abdominal radiography were unremarkable. On thoracic radiographs, a diffuse bronchointerstitial pattern with focal mineralization in the dorsocaudal lung fields was seen. Echocardiography did not reveal any clinically important abnormalities. Specifically, there was no evidence of cardiomyopathy, left atrial enlargement, or a thrombus.

At this time, thromboembolic disease was suspected, but the underlying cause was not clear. The cat was treated with lactated Ringer's solution (4 mL/kg/h [1.8 mL/lb/h], IV) and dalteparin (100 units, SC, q 24 h). Treatment with amoxicillin-clavulanate was continued (12.5 mg/kg, PO, q 12 h), and the dosage of prednisolone was decreased (1.25 mg/kg [0.56 mg/lb], PO, q 24 h). The cat's condition improved, and 4 days later, the left forelimb ataxia had nearly resolved, neurologic deficits were less marked, and blood flow in the left brachial artery could be documented.

Because signs of respiratory tract disease had not improved, bronchoscopy was performed. Excess mucus was seen in the lower airways, and cytologic examination of fluid obtained by means of bronchoalveolar lavage revealed a heavy background of mucus and debris with high cellularity (nucleated cell count, 4.74 X 10^7/L). Clumps of ciliated columnar epithelial cells predominated, although neutrophils and macrophages were also present. No bacteria were detected during examination of samples prepared by cytocentrifugation, and bacterial culture did not yield any growth.

Twenty-four hours later, the cat's condition deteriorated suddenly, and cardiopulmonary arrest quickly ensued. Despite attempts at cardiopulmonary resuscitation, the cat died shortly afterwards.

At necropsy, extensive consolidation of all lung lobes was observed. Examination of major arteries of the forelimbs and hind limbs, as well as the entire aorta and iliac bifurcation, did not reveal any gross abnormalities. Microscopically, the lungs contained multifocal, parenchymal infiltrations consisting of cuboidal to columnar neoplastic epithelial cells (Figure 1). In adjacent, grossly unaltered lung tissue, small accumulations of neoplastic cells were seen in small arterioles and capillaries. Bronchial lymph nodes contained small groups of neoplastic epithelial cells in subcapsular
sinuses. Neoplastic epithelial cells of similar morphology were identified in nodular masses in the muscle groups. Occasional intravascular tumor emboli were identified obliterating small and large arterioles (Figure 2). Representative sections of lung and muscle were stained for pan-cytokeratin antigen and factor VIII–related antigen. Neoplastic cells in pulmonary infiltrates, muscle metastases, and intravascular emboli displayed intense cytoplasmic staining for cytokeratin. Staining for factor VIII–related antigen confirmed that clusters of neoplastic cells represented intravascular emboli. Histologically, a diagnosis of a pulmonary papillary adenocarcinoma with intravascular metastases to forelimb and hind limb muscles and lymphatic metastases to bronchial lymph nodes was made.

An 11-year-old neutered female Persian cat was examined at the University of Liverpool Small Animal Hospital because of a sudden onset of right hind limb lameness. The cat had no history of previous illness, was currently vaccinated, and was allowed free access to the outdoors.

Physical examination revealed tachypnea (56 breaths/min), but no abnormalities were detected on thoracic or cardiac auscultation. The right femoral pulse was not palpable, and the right gastrocnemius muscle was firm and swollen. Palpation of the gastrocnemius muscle resulted in signs of pain. Skin temperature and color of the distal portions of the hind limbs were normal. Neurologic examination revealed an abnormal gait with knuckling of the right hind limb. Conscious proprioception and the patellar and withdrawal reflexes were diminished in the right hind limb, and pain sensation distal to the tarsus was absent. Results of a CBC, serum biochemical profile, and urinalysis were unremarkable. Cytologic examination of a fine-needle aspirate revealed dysplastic mesenchymal cells and sloughed necrotic neoplastic cells (arrow). H&E stain; bar = 200 µm.

The cat was treated with lactated Ringer’s solution (4 mL/kg/h, IV) and buprenorphine (10 µg/kg, IM, q 6 h). Six hours after admission, the right femoral pulse was palpable, and 24 hours after admission, the cat had regained normal use of the right hind limb and was discharged from the hospital.

One month later, the cat was reexamined because of similar clinical signs. On this occasion, the right gastrocnemius muscle was palpably normal, but the right quadriceps muscle was swollen and palpation elicited signs of pain. Results of cytologic analysis of a fine-needle aspirate were similar to previous findings. The right femoral pulse was palpable but weaker than the left femoral pulse. On the basis of the clinical signs and results of a neurologic examination, embolism was suspected, although the cause was unclear. Further diagnostic testing, including radiography and muscle biopsy, was suggested, but the owner declined, and the cat was treated with fluids IV, buprenorphine (10 µg/kg, IM, q 6 h), cyproheptadine (0.3 mg/kg [0.13 mg/lb], PO, q 8 h), and dalteparin (100 units, SC, q 24 h). There was no improvement during the next 7 days, and the cat was euthanatized at the owner’s request.

Figure 1—Photomicrograph of a section of lung from a cat with primary pulmonary adenocarcinoma and arterial embolization. Notice the papillary projections of neoplastic epithelial cells and sloughed necrotic neoplastic cells (arrow). H&E stain; bar = 200 µm.

Figure 2—Photomicrographs of sections of the gastrocnemius muscle from the cat in Figure 1. A) An intravascular tumor embolus surrounded by scirrhous reaction and scattered lymphocytes, plasma cells, neutrophils, and macrophages can be seen. H&E stain; bar = 200 µm. B) Immunohistochemical staining for factor VIII–related antigen highlights endothelial cells (arrows) lining small arterioles that contain densely packed pleomorphic epithelial cells, confirming that clusters of neoplastic cells represent intravascular emboli. Peroxidase-antiperoxidase reaction with Papanicolaou hematoxylin counterstain; bar = 200 µm.
At necropsy, all lung lobes were extensively consolidated, and the parenchyma contained multiple, randomly distributed, 2- to 34-mm-diameter nodules. Examination of major forelimb and hind limb arteries did not reveal any abnormalities. Multifocal, well-circumscribed, pale-tan, firm, nodular masses were seen in the semitendinosus, semimembranosus, quadriceps femoris, gastrocnemius, and adductor muscles.

Microscopically, there was multifocal infiltration of the lung parenchyma with cuboidal to low columnar neoplastic epithelial cells forming distinct tubular structures (Figure 3). Tumor cells were also seen in small alveolar capillaries, and regional bronchial lymph nodes contained small groups of neoplastic epithelial cells in afferent lymphatics and subcapsular sinuses and throughout the cortex. Histologic examination of portions of the gastrocnemius muscle revealed similar neoplastic infiltrates with a marked scirrhous reaction (Figure 4). Immunohistochemical staining of pulmonary and muscular tissue for pan-cytokeratin antigen revealed intense cytoplasmic staining of neoplastic cells. Staining for factor VIII–related antigen confirmed that clusters of neoplastic cells represented intravascular emboli. Histologically, a diagnosis of a pulmonary bronchoalveolar carcinoma with lymphatic metastases to bronchial lymph nodes and intravascular metastases to hind limb muscles was made.

Thromboembolic disease is common in cats. Inappropriate thrombus formation in a portion of the cardiovascular system is followed by partial thrombus dissolution and dissemination of emboli via the circulation. These emboli then lodge in a variety of sites, depending on vascular anatomic features and embolus size. Sites predisposed to lodgment of emboli include the aortic trifurcation and smaller vessels, such as the femoral, brachial, mesenteric, and cerebral arteries. Thrombotic tendencies are recognized in both human and small animal patients with cancer, and thromboembolism is common. Similarly, venous embolization of malignant tumors is common, and pulmonary neoplastic emboli have been identified in patients with a variety of tumors but are predominantly associated with carcinomas.14 In contrast, peripheral arterial tumor embolization is an unusual manifestation of neoplastic disease and a rare cause of acute arterial occlusion in human and veterinary medicine.6,11 Only tumors with access to the pulmonary venous system, the cardiac chambers, or the aorta can cause arterial tumor embolization.

Tumor embolization may occur as part of the metastatic process. Metastasis is thought to be a multistep process14 that begins when a tumor establishes a capillary network from the surrounding host tissue. Neoplastic cells then produce lytic enzymes, allowing invasion of these blood vessels and access to the systemic circulation. Tumor cells that enter the systemic circulation are subject to host immune and nonimmune defenses, and those that survive the host's defenses travel as cell aggregates to the capillary beds of distant organs, where they adhere to the vessel wall. Finally, extravasation can then lead to growth of metastases.
Most tumor cell aggregates consist of small numbers of cells, and these microemboli do not commonly cause clinical signs related to vessel occlusion. Larger fragments of tumor may break off from tumors that have eroded into larger vessels, but again these typically are not associated with clinical signs of vessel occlusion.

Several reports describe cats with primary pulmonary tumors that developed intravascular metastases. In most of these reports, the tumor metastasized to the digits, presumably as a result of tumor emboli passing into the small arteries supplying the digits. However, what these reports should be targets for pulmonary metastases remains unclear. In human patients with primary lung tumors, most bone metastases occur proximal, rather than distal, to the knee and elbow joints. However, in human patients with digital metastases, the dominant hand seems to be more commonly affected, possibly reflecting the greater blood flow in the dominant hand. Similarly, it has been hypothesized that the reason for the distinctive pattern of digital metastases in cats with primary lung tumors is the vascular architecture of the digital pads, which is required to allow heat loss. Presumably, in the 2 cats described in the present report, tumor emboli were larger and lodged in small and large arterioles in the limb muscles, never making it to the small arteries supplying the digits.

In previous reports of cats with primary pulmonary tumors that metastasized to the digits, signs of metastatic disease were evident before signs of respiratory tract disease developed, and none of these cats were examined because of respiratory tract disease. Similarly, why the digits should be targets for pulmonary metastases remains unclear. In human patients with primary lung tumors, most bone metastases occur proximal, rather than distal, to the knee and elbow joints. However, in human patients with digital metastases, the dominant hand seems to be more commonly affected, possibly reflecting the greater blood flow in the dominant hand. Similarly, it has been hypothesized that the reason for the distinctive pattern of digital metastases in cats with primary lung tumors is the vascular architecture of the digital pads, which is required to allow heat loss. Presumably, in the 2 cats described in the present report, tumor emboli were larger and lodged in small and large arterioles in the limb muscles, never making it to the small arteries supplying the digits.

In previous reports of cats with primary pulmonary tumors that metastasized to the digits, signs of metastatic disease were evident before signs of respiratory tract disease developed, and none of these cats were examined because of respiratory tract disease. Similarly, why the digits should be targets for pulmonary metastases remains unclear. In human patients with primary lung tumors, most bone metastases occur proximal, rather than distal, to the knee and elbow joints. However, in human patients with digital metastases, the dominant hand seems to be more commonly affected, possibly reflecting the greater blood flow in the dominant hand. Similarly, it has been hypothesized that the reason for the distinctive pattern of digital metastases in cats with primary lung tumors is the vascular architecture of the digital pads, which is required to allow heat loss. Presumably, in the 2 cats described in the present report, tumor emboli were larger and lodged in small and large arterioles in the limb muscles, never making it to the small arteries supplying the digits.

None of the previous reports of cats with metastatic pulmonary carcinomas describe signs of arterial occlusion. A report of 16 cats with bronchogenic carcinoma that had metastasized to a digit did describe 1 cat that died of presumptive congestive heart failure and aortic thromboembolism. However, no histologic examinations were performed to determine whether clinical signs were a result of cardiac-related or tumor-related thromboembolism. A second cat in that report had flaccid hindlimb paralysis, but no mention was made of whether femoral pulses were palpable. Thus, it is possible that these cats had arterial tumor embolization.

Similarly, other reports of arterial thromboembolism in cats may have included cats that in fact had arterial tumor embolization. In a study of 127 cats with arterial thromboembolism, 6 were confirmed to have neoplasia, including 2 with pulmonary carcinoma, and 1 had neoplastic cells in the thrombus. Similarly, a review of 46 cats with arterial thromboembolism treated with streptokinase described 1 cat determined at necropsy to have neoplasia of the aorta, and a review of 100 cats with arterial thromboembolism described 3 cats in which pulmonary masses were found. Two of these cats had coexisting cardiac disease, but the third had no cardiac abnormalities. Postmortem examinations were not carried out, and it is possible that clinical signs in these cats were a result of arterial tumor embolization, rather than thromboembolic disease. Finally, a report of a cat with bronchoalveolar carcinoma and arterial thromboembolism suggested that emboli were a result of neoplastic thromboembolysis. However, emboli were not examined histologically. Therefore, it is possible that they may have been tumor emboli.

Tumor emboli are documented more frequently in the human literature than in the veterinary literature. Venous embolization of malignant tumors is not uncommon, but arterial embolization by neoplastic cells is rare. To our knowledge, only 105 cases of peripheral embolization with neoplastic emboli have been published in the human literature in the past 100 years. Most of these cases involved patients with primary or secondary lung tumors and aortic tumors, and in many instances, embolization occurred at the time of pulmonary tumor resection. Other tumors reportedly associated with arterial embolization include tumors of the gastrointestinal tract, thyroid gland, larynx, pharynx, breast, kidney, and adrenal gland; tumors were of various histologic types, including sarcomas, carcinomas, melanomas, and malignant histiocytomas. The most common sites of embolization are the lower extremity arteries and the cerebral circulation. These patients are often candidates for balloon catheter embolectomy, with a reported success rate (ie, return of organ function) of 84%. The fact that both cats in this report were Persians is interesting, as this breed represents a small percentage of the hospital cat population. Three cats with pulmonary neoplasia and digital metastases described in previous reports were also Persians. A study of 86 cats with primary lung tumors reported that only 6 were Persians, but whether Persians were overrepresented, compared with the hospital population, was not reported. If there truly is an increased rate of metastatic pulmonary neoplasia in Persian cats, this could reflect either an increased incidence of primary pulmonary tumors or a greater tendency for metastatic disease in this breed. Further studies on the incidence of pulmonary tumors in Persians would be useful.

Clinical signs in the cats in the present report were a result of arterial occlusion by tumor emboli and were similar to those seen in cats with arterial thromboembolism secondary to cardiac disease. Although uncommon, tumor embolization should be considered in cats with clinical signs of systemic arterial embolism in which cardiac disease has been ruled out.

References


1068 Scientific Reports: Clinical Report
JAVMA, Vol 225, No. 7, October 1, 2004


