Vaccine Site-Associated Sarcoma and Malignant Lymphoma in Cats: A Report of Six Cases (1997-2002)

Six cats developed malignant lymphoma 3 to 45 months after treatment for vaccine site-associated sarcoma. During the same time period, 184 cats were evaluated in the teaching hospital for vaccine site-associated sarcomas. Feline vaccine site-associated sarcoma is not believed to be associated with feline leukemia virus (FeLV) infection. Five of six cats were negative by enzyme-linked immunosorbent assay for FeLV antigens at the times of diagnosis of both sarcoma and lymphoma, and no cats were infected with feline immunodeficiency virus. **J Am Anim Hosp Assoc 2004;40:47-50.**

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Introduction

Feline vaccine site-associated sarcoma is a unique tumor of cats first described by Hendrick in 1991.[1] Although known to arise at sites of vaccination, the etiopathogenesis remains enigmatic. For some cats with vaccine site-associated sarcoma, treatment is curative, but other cats develop local tumor recurrence or metastasis after treatment. The authors are aware of one previous publication describing a cat with vaccine site-associated sarcoma that subsequently developed malignant lymphoma.[2] Reported here are cases of six cats seen between 1997 and 2001, at the University of California Veterinary Medical Teaching Hospital (VMTH), for lymphoma that developed 3 to 45 months after treatment for vaccine site-associated sarcomas. For all cats, vaccination history, tumor site, and histopathological findings were consistent with vaccine site-associated sarcomas, as described elsewhere.[3,4]

Case Reports

Case No. 1

A 14-year-old, 5.1-kg, neutered male domestic shorthair (DSH) cat was examined at the VMTH after the referring veterinarian had surgically removed a 2 cm-diameter fibrosarcoma at a vaccination site. Because histopathological examination revealed that the deep borders of the tumor approached within 7 mm of the cut edge, the cat was referred for additional treatment considerations. Upon admission, a surgical scar 12 cm in length was present, extending laterally across the left shoulder and back. Enzyme-linked immunosorbent assay (ELISA) for feline leukemia virus (FeLV) was negative, and the antibody test for feline immunodeficiency virus (FIV) was also negative. Computed tomography (CT) did not reveal local tumor recurrence or pulmonary metastases; regardless, the size and complexity of the surgical site precluded radiation treatment. Alternatively,

the cat was given adjuvant chemotherapy with carboplatin (six treatments; 10 mg/kg body weight, intravenously at 21-day intervals). At completion of the treatment period, repeated CT did not reveal recurrence of fibrosarcoma. Seven months after diagnosis of vaccine site-associated sarcoma, the cat was diagnosed with diabetes mellitus, which was partially regulated with insulin. Sixteen months after diagnosis of vaccine site-associated sarcoma, the cat was losing weight. An irregularly contoured, 4 cm-diameter mass of mixed echogenicity was detected by ultrasonography in the cat's midabdomen and was adherent to small bowel loops. Ultrasonography was used to guide an 18-gauge biopsy needle into the mass; histopathology of the biopsy specimen revealed gastrointestinal (GI) lymphoma. Staging procedures confirmed alimentary lymphoma affecting small bowel and mesenteric lymph nodes. Blood tests for FeLV and FIV were repeated and were negative. The cat was given chemotherapy for lymphoma using multiple drugs (i.e., vincristine, cyclophosphamide, prednisone, doxorubicin) as outlined elsewhere,[5] and although some measurable reduction in the size of the tumor was recorded, the treatment duration for lymphoma was brief (16 weeks). The cat was euthanized 19 months after diagnosis of vaccine site-associated sarcoma because of acute onset of central nervous system (CNS) signs. At necropsy, malignant lymphoid cells were detected in the brain, stomach, heart base, kidney, urinary bladder, and lung. There was a meningioma in the third ventricle of the brain. Adenocarcinoma and islet amyloidosis were identified in the pancreas. There was no recurrence of fibrosarcoma. Immunohistochemistry for lymphocyte markers confirmed T-cell lymphoma (CD3, reactive; CD79, negative).

Case No. 2

An 11-year-old, 5.3-kg, neutered male DSH cat was examined because of an irregular, 3 cm-diameter mass in the deep soft tissues between the scapulae. Blood tests for FeLV and FIV were negative. Computed tomography revealed a contrast-enhancing subcutaneous (SC) mass in the right dorsal thorax extending from the third to sixth thoracic vertebrae, in intimate contact with the right epaxial musculature and juxtaposed to the dorsal aspect of the right scapula and spinous processes of the vertebrae. Incisional biopsy revealed vaccine site-associated fibrosarcoma. The tumor volume was treated with megavoltage irradiation (16 fractions, 3 Gy/fraction, to a total dose of 48 Gy given over a 21-day period), and after the course of radiation therapy, the tumor was removed surgically. Eight months later, a thoracic radiograph was done, and a well-defined nodule was detected in the right caudal lung lobe. An ultrasound-guided, fine-needle aspirate was collected for cytopathology, and groups of malignant-appearing mesenchymal cells were obtained. Ultrasonography of the abdomen revealed a focal, thickened loop of small intestinal bowel. A right caudal lung lobectomy was done via thoracotomy, and full-thickness bowel wall biopsies were collected from the thickened bowel region localized to the jejunum on celiotomy. The lung mass was interpreted histopathologically as fibrosarcoma, presumed to be metastatic from the original SC tumor. The small intestine contained a lymphoma; immunohistochemical staining of the tumor confirmed the T-cell phenotype. The owners declined chemotherapy for the lymphoma, but the cat was given prednisone. One week after surgery, the cat had thromboembolism in the right pelvic limb that was attributable to preexisting hypertrophic cardiomyopathy. The cat was euthanized, and a necropsy was not done.

Case No. 3

A 14-year-old, 4.3-kg, spayed female DSH was treated surgically by the referring veterinarian for a 3 cm-diameter mass in the deep soft tissues of the left shoulder and interscapular region of the back. The tumor was interpreted histopathologically as vaccine site-associated fibrosarcoma. The tumor extended to the deep surgical margins. The cat was treated with broad excision of the surgical scar at the VMTH, and following healing, the surgical site and surrounding tissues were irradiated with megavoltage (16 fractions, 3 Gy/fraction, to a total of 48 Gy given over a 21-day period). The cat was not seen until 45 months later when it was examined because of generalized peripheral lymphadenopathy. In addition, a sternal lymph node was enlarged on thoracic radiographs, and abdominal ultrasonography revealed an enlarged liver, spleen, and mesenteric lymph nodes. Blood tests for FeLV and FIV were negative. Cytopathology of a fine-needle aspirate of a prescapular lymph node revealed poorly differentiated lymphoid cells and lymphoblasts. The owner declined treatment for the cat, and it died 4 weeks later. Necropsy examination revealed lymphoma affecting the spleen, lymph nodes, liver, pancreas, mesentery, and SC tissues and musculature at the site of the previously treated fibrosarcoma [Figures 1, 2]. Immunohistochemistry confirmed the T-cell phenotype of tumor cells. There were bilateral, diffuse, nonfunctional thyroid adenomas.

Case No. 4

A 12-year-old, 7.2-kg, domestic longhair neutered male cat had diabetes mellitus that was regulated with insulin. The cat was treated surgically for a 2-cm (greatest diameter) tumor affecting the left lateral body wall caudal to the scapula. The tumor was interpreted histopathologically as vaccine site-associated fibrosarcoma. The tumor extended to the deep margins of the surgical resection, but additional therapy was declined by the owner. Blood tests for FeLV and FIV were negative. Three months after surgery, the cat was examined because of weight loss and palpable recurrence of tumor in the interscapular region. At that time, the cat was azotemic. Ultrasonography of the abdomen showed bilaterally enlarged kidneys with irregular contours. Aspiration and cytopathology of the kidneys revealed a monomorphic population of lymphoblasts. The blast cells were medium-sized, with basophilic cytoplasm and discrete vacuoles, moderately coarse nuclear chromatin, and large nucleoli indicating lymphoma. Immunohistochemistry was not done, as there was not sufficient material from the aspirate. The cat was given chemotherapy,[5] but it died within 4 weeks because of progressive uremia. A necropsy examination was not done.

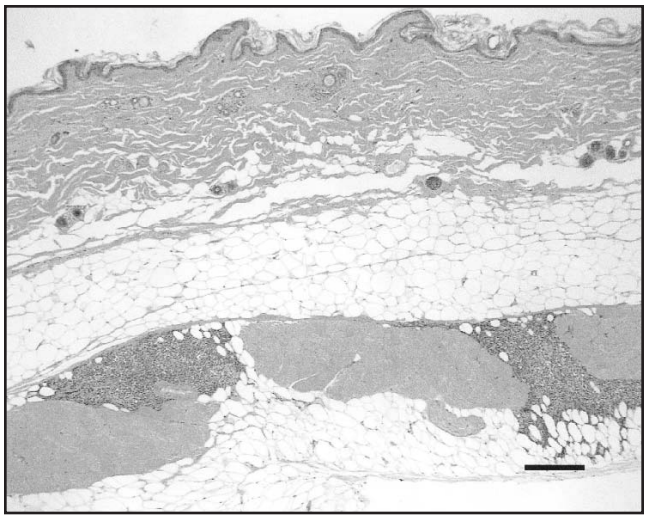

Figure 1—Malignant lymphoma invading superficial musculature (i.e., panniculus) and adipose tissue in dorsal scapular skin region of case no. 3 (Hematoxylin and eosin stain; bar=250 µm).

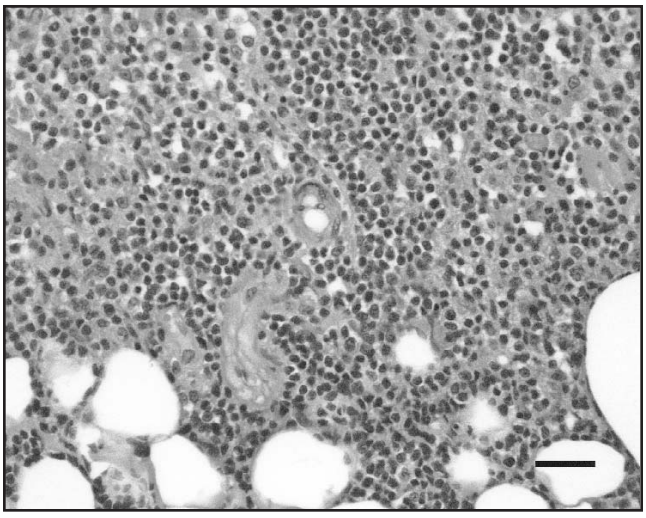

Figure 2—Higher magnification of lymphoma from the cat in Figure 1, showing mixed population of lymphoblastic and mature lymphocytic cells (Hematoxylin and eosin stain; bar=30 µm).

Case No. 5

A 10-year-old, 5.0-kg, neutered male DSH cat was treated surgically for an irregular, 6.6 cm-diameter vaccine site-associated sarcoma affecting SC tissues between the scapulae on the cat's back. Following surgery, the cat was given megavoltage irradiation (18 fractions, 3 Gy/fraction, to a total dose of 54 Gy given over a 23-day period). Sixteen months later, the cat had chronic diarrhea and occasional vomiting. Ultrasonography revealed mesenteric lymphadenopathy. Endoscopy of the stomach and duodenum was done; the duodenal mucosa appeared edematous and thickened. Biopsy of the duodenum revealed expansion of the lamina propria and submucosa with a monomorphic cellular infiltrate diagnostic for lymphoma. Immunohistochemistry confirmed the T-cell phenotype of tumor cells. Blood tests for FeLV and FIV were negative. The cat was treated with prednisone and chlorambucil, and it survived an additional 8 months. A necropsy examination was not done.

Case No. 6

An 8-year-old, 6.0-kg, neutered male domestic medium-hair cat was examined because of a 3-cm (greatest diameter) mass in the deep soft tissues over the cranial aspect of the left shoulder region. Computed tomography revealed a contrast-enhancing mass in the SC tissues over the left scapula without obvious invasion of the underlying musculature. Surgical excision was done, and histopathology revealed complete excision of an unencapsulated, vaccine site-associated fibrosarcoma. The cat was given no additional treatment. Forty-three months later, the cat was examined because of lethargy and weight loss of several weeks' duration and recent onset of grand-mal seizures. The cat was pancytopenic, and there were unclassified cells in the peripheral blood. Enzyme-linked immunosorbent assay for FeLV was positive, but the antibody test for FIV was negative. Abdominal ultrasonography revealed hypoechoic hepatic masses, subcapsular renal masses, and a small intestinal mass. Fine-needle aspirates for cytopathology of the liver and small intestinal masses showed lymphoblasts. The cat was euthanized at the owner's request before further workup (including a bone-marrow examination) could be done. Necropsy examination confirmed lymphoma affecting liver, ileum, and kidneys. Immunohistochemistry confirmed a B-cell phenotype of the tumor cells. No lesions on gross or histopathological examination were identified in the CNS, and the cause of the seizures was thought to be of a metabolic nature secondary to liver and renal damage.

Discussion

Whether or not vaccine site-associated sarcoma increases the risk for lymphoma is unknown. It is tempting to think that the factor(s) favoring the development of sarcoma in the cat might be similar to whatever factor(s) increase the risk for lymphoma. Causal factors might include reactivation of a previously latent FeLV infection, carcinogenesis resulting from chemotherapy or irradiation, immune system dysregulation or suppression, and activation of oncogenes or inactivation of tumor-suppressor genes. None of these possibilities were tested in the six cats detailed in this study.

It has been estimated that sarcomas develop in cats at a rate of 0.63 per 10,000 doses of vaccines given.[6] From 1997 to 2001, 8,197 cats were examined at the VMTH; of these, 1,755 had cancer, and 777 had lymphoma. During this same time period, there were 184 cats examined at the VMTH with sarcomas presumably related to vaccination based on anatomical site, histopathological description, and vaccination history.

Most of these cats with vaccine site-associated sarcomas had received at least surgical treatment, whereas others had combinations of surgery, radiation therapy, or chemotherapy. Of those 184 cats, the authors are aware that six subsequently developed lymphoma, and 17 other tumors were diagnosed in these cats either simultaneously with, or subsequent to, the diagnosis of fibrosarcoma. Those tumors represented a variety of histopathological types and anatomical locations with no unifying features.

Of the six cats studied, one had local tumor recurrence of the vaccine site-associated sarcoma during the 3 to 45-month period of evaluation, and one cat developed pulmonary metastasis. Two cats had diabetes mellitus.

Feline vaccine site-associated sarcoma is not believed to be associated with FeLV infection.[7] In the present study, of the five cats tested for FeLV and FIV at the time of diagnosis of fibrosarcoma, none were infected. Of the six cats tested at the time of diagnosis of lymphoma, one was infected with FeLV, and all six cats were negative for antibodies to FIV. It is conceivable that more sensitive tests for retroviruses (e.g., immunofluorescence [IFA], feline oncornavirus-associated cell membrane antigen [FOCMA], Western blot, or polymerase chain reaction) may have detected FeLV. In one recent study, only two (2%) of 107 cats with lymphoma were FeLV-positive using ELISA to detect p27 antigen in serum, whereas 25 (26%) of 97 cats contained FeLV deoxyribonucleic acid when polymerase chain reaction detection methods were used.[8]

A characteristic feature of vaccine site-associated sarcomas is peritumoral aggregates of lymphocytes, a large proportion of which are T lymphocytes.[9] It is conceivable that those inflammatory aggregates could represent a milieu of cells susceptible to transformation after exposure to appropriate initiators. The demonstration in case no. 3 of lymphoma in deep connective tissues at the site of previous vaccine site-associated sarcoma and radiation therapy raises this possibility.

Treatment methods used for vaccine site-associated sarcoma might also increase the risk for the subsequent development of lymphoma. In the cats studied, features common to these six cats were anesthesia and surgery; three of six cats were given radiation therapy; and one was given chemotherapy as part of the treatment prescription for vaccine site-associated sarcoma.

This is a small case series involving two relatively common tumors in cats. It is possible that the diagnoses of fibrosarcoma and lymphoma are entirely coincidental and that there was no relationship between the development of these two seemingly independent neoplasms. Seventeen other second neoplasms were identified in the 184 cats diagnosed with vaccine site-associated sarcoma in the VMTH during the same time period. Further study of a large number of cats would be required to establish a link, if any, between vaccine site-associated sarcomas and other neoplasms.

One cat (case no. 1) had vaccine site-associated fibrosarcoma, lymphoma, meningioma, and pancreatic adenocarcinoma, and one cat (case no. 3) had bilateral thyroid adenomas. In the dog, it has been demonstrated that diagnosis of tumor, either benign or malignant, increases the risk for subsequent development of new tumors of the same or other histopathological types.[10] The authors are not aware of a similar study focusing on feline tumors.

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