Cut Meowt

A Case Report of Injection-site Sarcoma in a Cat

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Introduction

Over twenty years ago the association between vaccine administration and soft tissue sarcomas in cats was first discovered. These tumors were thought to correlate with the sharp increase of the number of cats vaccinated for rabies and the introduction of the FeLV vaccine. Termed 'vaccine-associated sarcomas' many groups have joined forces to find not only the best treatment options but also the best prevention as a cure has yet to be discovered (1). With the discovery of these tumors also being related to non-vaccine injections such as long acting steroids and antibiotics, lufernuron, and microchips, these tumors of injection site origin are now termed injection-site sarcomas (ISS) or feline injection-site sarcomas (FISS) (1).

Injection-site sarcomas arise in areas that are common sites of vaccine administration, often the scapular, intrascapular, and lateral thigh regions. Although common in cats they are rare in other species. Injection-site sarcomas are of mesenchymal origin with the most frequent occurrence being fibrosarcomas with malignant fibrous histiocytomas, osteosarcomas, chondrosarcomas, and other types being reported (2). There is no sex predilection, but age does seem to have a bimodal distribution with peaks at 6-7 years and 10-11 years. Treatment is centered around complete excision of the mass with radiation, chemotherapy, or immunotherapy as additions for a multimodal approach (2). The purpose of this case report is to describe the management of one case of an injection-site sarcoma in a 14-year-old Domestic Shorthair with an amputation and IL-2 treatments.

Case Summary

An approximately 14-year-old male neutered tuxedo Domestic Shorthair cat presented to Mississippi State University College of Veterinary Medicine (MSU-CVM) Surgery Service on

August 28, 2017 for surgical planning for a right forelimb amputation. Prior to his surgical consult, an extensive diagnostic workup had been performed by the MSU-CVM Oncology department revealing the diagnosis of an injection-site fibrosarcoma of anaplastic variant.

The patient originally presented to his primary veterinarian after his owner noticed a mass on the patient's right shoulder on August 8, 2017. The patient had been vaccinated on February 11, 2017 with FeLV/ FVRCP and rabies vaccines. He had no previous medical problems and was not on any medications. He was an indoor only cat who lived with one other cat that lived mainly outdoors. Radiographs were performed and showed no bony involvement. He was then referred to MSU-CVM Oncology Service for further diagnostics.

On August 14, 2017 the patient presented to the MSU-CVM Oncology Service for a full diagnostic workup of the right forelimb mass. This workup included bloodwork, urinalysis, radiographs, an incisional biopsy, and computed tomography (CT). An echocardiogram was also performed due to the presence of a grade III/VI heart murmur. The patient's CBC revealed a mildly elevated MCV 61.3 fL (40-55.0), a mildly elevated MCH 18.2 pg (13.0-17.0), a moderate thrombocytopenia 157 K/uL (200-700), and low eosinophil percentage 1% (2-12). A manual platelet count revealed a platelet estimate number of 416 indicating that the patient had sufficient platelets and was not thrombocytopenic. The serum chemistry revealed a mild hypercholesterolemia 211mg/dL (95-200), and his total T4 was mildly low at 1.8 ug/dL (2.0-5.0). The patient's urinalysis was unremarkable. The patient's radiographs showed cardiomegaly, enlarged caudal pulmonary lobar arteries, spondylosis deformans, and no evidence of nodular pulmonary metastasis. The cardiomegaly was characterized by contact with the diaphragm, rounding of the atrioventricular region, and the cardiac silhouette occupying greater than 50% of the width of the thoracic cavity on the VD projection. An echocardiogram

revealed thickening of the left ventricular wall, elevated fractional shortening, and left ventricular outflow tract turbulence likely due to hypertrophic cardiomyopathy. The incisional biopsy was performed under sedation with samples being sent for histopathological examination. The incisional biopsy results revealed a histiocytic panniculitis and anaplastic sarcoma. The CT showed an irregularly shaped mass approximately 7.4 cm x 4.5 cm x 5.3 cm in size of soft tissue dense material, as well as enlarged right superficial cervical and right axillary lymph nodes. The mass extended cranial to the right shoulder and humerus to the tissues lateral to the caudal aspect of the right scapula. It was contrast-enhancing with more defined margins on the arterial phase post-contrast series. There was an ill-defined contrast enhancing area extending from the mass to the musculature ventromedial to the scapula.

Due to the recent vaccine history and nature of the mass it was tentatively diagnosed as a injection-site sarcoma. The patient was discharged from MSU-CVM on tramadol 50mg orally BID, and gabapentin 20mg orally once daily with a schedule to return and pursue amputation and feline interleukin-2 (IL-2) treatments. Radiation therapy was declined as a treatment option for this patient.

The patient returned to the MSU-CVM Oncology service on August 22, 2017 for his first Oncept IL-2 treatment. The IL-2 injections were given subcutaneously in the pattern determined by the manufacturer. This pattern consisted of five injections (0.2mls each) given at the four corners of a 5 x5 cm square around the mass and the center of the four corners (or center of mass). The patient was then discharged to return one week later for a surgical consult.

The patient then presented to MSU-CVM Surgery Service on August 28, 2017 for surgical planning for a right forelimb amputation. On examination, the patient was quiet, but bright and alert. He weighed 6.4kg with a body condition score of 6/9. He was moderately

tachycardic and tachypneic (heart rate of 240 beats per minute, and respiratory rate of 88 breaths per minute). His temperature was on the higher end of normal (102.2˚F). The patient had a III/VI heart murmur prominent parasternal. He also had increased lung sounds in all lung fields. The patient had a firm, nodular, irregularly marginated, adhered mass on his right shoulder starting proximal to the shoulder spanning distally to midway of the humerus. The biopsy site had a moderate amount of purulent discharge. The remainder of his physical examination was unremarkable.

A right forelimb amputation with implantation of a soaker catheter was performed on August 29, 2017. A 'Big 4' was performed before anesthesia. The results run in clinic were PCV 26, total protein 8.4, BUN (azostick) 5-15, and glucose 125. The normal approach to a forelimb amputation was not pursued due to the extensive nature of the mass and draining tract from the incisional biopsy. A sterile marker pen was used to mark the circumferential edges of the mass. A sterile ruler was then used to measure 3 cm from the mass edges to ensure sufficient margins were obtained and an outer circle was marked. Electrocautery was used to dissect through the musculature and all vessels medial to the scapula were ligated with suture. The brachial plexus was separated, and the nerves were individually injected with Bupivicaine 5% in the perineurium before being dissected. The scalenus muscle was removed from the thoracic wall to achieve ideal facial plane depth beneath the mass tissue. The leg was removed and submitted post-operatively for histopathology. A soaker catheter was placed during closure of the subcutaneous tissue and the skin was closed. The patient was maintained in ICU overnight on a fentanyl CRI (2.5 mcg/kg/hr), bupivacaine via soaker catheter (1ml q8h), and Clavamox (75mg orally BID). On the morning of August 30, 2017, the patient was moved to the surgery wards. He was then maintained on bupivacaine via soaker catheter (1ml q8h), Clavamox (75mg orally BID), and

buprenorphine trans-buccally (0.12mg q8h). The patient was also administered mirtazapine (3.75mg) every 24 hours to encourage him to eat. The patient was discharged 4 days after surgery. Histopathologic evaluation confirmed the diagnosis of an injection-site fibrosarcoma. Although the mass was excised with 'clean' margins there were neoplastic cells invasive into the muscle along the surgical margin classifying the amputation with narrow margins.

On September 5, 2017 the patient presented to his primary veterinarian for his second IL-2 injection. On September 11, 2017 the patient presented to the MSU-CVM Oncology service for his third IL-2 injection and to remove his sutures. His incision was clean, and not red or swollen. The sutures were removed. The patient was sedated and administered his Il-2 injections. The fourth and fifth IL-2 injections were administered at the patient's primary veterinarian's office on September 18, 2017 and September 25, 2017 respectively.

On October 9, 2017 the patient returned to MSU-CVM Oncology service to receive his last IL-2 injection. He was discharged with instructions to monitor the amputation site for regrowth of the mass, and to have thoracic radiographs performed at his primary veterinarian every three months to screen for metastasis. It was suggested to administer future vaccines only if medically necessary and only on the tip of the tail for easier surgical excision if an injection-site sarcoma were to develop.

On January 9, 2018 the patient returned to MSU-CVM Oncology service to re-stage the previously excised fibrosarcoma. Thoracic radiographs were taken showing a diffuse structured interstitial pattern of the pulmonary parenchyma, and a missing right scapula and leg due to the previous amputation. Previously noted cardiomegaly and spondylosis deformans were present. The top differential for the structured interstitial pattern was metastasis of the previously

diagnosed fibrosarcoma. The patient was discharged with gabapentin (20mg), mirtazapine and considerations for quality of life care.

Discussion

Feline injection-site sarcomas (FISS) are soft tissue sarcomas of mesenchymal cell origin. Although they can be many different histotypes, fibrosarcomas are the most commonly documented with malignant fibrous histiocytomas, osteosarcomas, chondrosarcomas, rhabdomyosarcomas, and undifferentiated sarcomas also reported in the literature (3). The occurrence of FISS is found to be anywhere from 1.3/ 1000 vaccinations to 1/10,000 vaccinations (7, 10). The range correlates with the sharp increase in vaccinations given to cats starting in the late 1980's with legally mandated rabies vaccinations and new vaccines on the market for feline leukemia virus (FeLV). FeLV and rabies vaccines are the most documented vaccines given in sites before diagnosis of FISS (12).

Retrospective studies have shown that cats given multiple vaccines (2 or more) in the same location have over a 120% higher risk of developing an associated sarcoma than a cat who was not given any vaccines. There are proposed genetic correlations due to familial associations as siblings tend to be more likely to develop FISS than unrelated cats. Also cats who have developed one FISS are more likely to develop another FISS (7). The average time from vaccine exposure to tumor formation is 3 months to 3 years although up to 10 years post vaccination has been documented (8, 10). Although FISS are found to be locally aggressive they have a low metastatic rate of approximately 25% with some studies proposing increased metastatic rates based on the survival time of the cat (8).

Alterations in the genes responsible for p53 (protein factor that regulates the cell cycle of tumor cells) have been proposed to correlate to the prevalence of FISS in cats (8). Likewise, cytokines, transforming growth factor-β (TGF-β) and basic fibroblast growth factor (FGF-b), responsible for certain types of sarcomas in chickens and humans may also play a role in the development of FISS as they are commonly found in samples examined by immunohistochemistry (8, 1). Temperature of the vaccine at administration was shown in one study to affect incidence of sarcoma formation with cold vaccines more likely to lead to FISS (8).

FISS have characteristic histologic findings of an inflammatory response on the periphery as well as marked nuclear and cellular pleomorphism, high mitotic activity, and large zones of necrosis. These are all consistent with an aggressive tumor behavior. The areas of chronic inflammation have proliferating fibroblasts and myofibroblast that represent a stage during the process of wound healing that is consistent with an abnormal response to a traumatic event. This presence of an inflammatory response remains as large numbers of follicular aggregates of lymphocytes and lesser numbers of plasma cells that are normally found around the periphery of the mass (1, 12). Zones of transition, from inflammatory granuloma to sarcoma, are often found suggestive of the inflammatory response to the vaccination (or other subcutaneous injection) eventually leading to the formation of a sarcoma (6, 10).

Within and around the sarcomas are large macrophages with blue-gray cytoplasm, which is presumed to be phagocytosed adjuvant material from the vaccinations. Historically aluminum adjuvants were suggested to be a causative agent of the inflammatory response and resulting tumor formation due to their presence in histologic samples (1). Further research has shown that vaccines with non-aluminum adjuvants as well as nonadjuvanted vaccines pose a risk for

sarcoma formation (1, 3). Areas of necrosis surrounded by granulation tissue is found at the vaccine administration site within the central area of the mass (1, 10). Multinucleated giant cells are found in FISS but are not associated with nonvaccine sarcomas (1).

Diagnosis of an FISS starts with a thorough history and physical examination. Injection histories should include when the cat received the injection, where the cat received the injection, and the vaccine or medication administered. The Vaccine-Associated Feline Sarcoma Task Force (VAFSTV) recommends that every mass that fits a three-tier criterion should be biopsied. The three-tier criterion or the "3-2-1 rule" includes 1) a mass that is still growing after 1 month 2) a mass that is larger than 2 cm and 3) a mass that persists for more than 3 months (8, 9). After determining that a mass should be further investigated a fine needle aspirate with cytologic evaluation is the first step in diagnosis. Fine needle aspirates of FISS are diagnostic in 50% of cases leading to incisional biopsy as the main-stay of definitive diagnosis (8).

Incisional biopsy, the gold standard in diagnosis of FISS, is greatly preferred over excisional biopsy due to the low rate of clean margins obtained without advanced diagnostic imaging and surgical planning. An aggressive first surgery or pre-surgical radiation lead to better post-operative outcomes and better median survival times than treating a recurrence due to not obtaining margins on the first excision (8, 12). Incisional biopsies should be done in an area that does not further expand the surgical area. Histologic findings of the incisional biopsies that point to injection-site sarcomas versus other soft tissue sarcoma types in cats include peripheral inflammation with lymphocytes and macrophages, granulation tissue, and multinucleated giant cells (8).

There is no cure for FISS with treatment centered around delaying recurrence and metastasis. The first line of treatment which is arguably the most important factor in recurrence

rate and survival time is full excision of the mass with wide margins (8, 9). Use of advanced diagnostic imaging such as CT or MRI has been proposed to give the most accurate surgical planning dimensions of the tumors. Unlike some tumors FISS tend to have lateral projections that are not easily palpated but can be visualized on CT with contrast medium (2). Excisional margins should be at least 3-5 cm into healthy tissue and two facial planes beneath the tumor. Due to the wide surgical margins amputation of limbs and spinous vertebral processes and removal of epaxial muscles or thoracic wall tend to be part of the surgical plan. Disease-free intervals (DFI) of cats with complete surgical excision is found to be greater than 16 months (7, 8). The recurrence rate in cats with radical complete surgical margins is 19-22% compared to incomplete margins at 58-69% (7, 13).

Multimodal therapy has shown prolonged DFI and survival times in cats. The addition of radiation therapy to wide surgical excision can prolong survival times with medial survival time being 1.5-3.5 years (8, 9). Radiation therapy can be started prior to surgical excision and continued after the incision has healed (8). Radiation therapy prior to surgery may increase the effectiveness of a surgical excision due to the act of slowing down progression of the tumor at the margins (12). Chemotherapy may be added to the multi-modal approach although it has not been thoroughly evaluated for its efficacy in use for FISS. The most commonly used chemotherapeutic agents are doxorubicin, carboplatin, and cyclophosphamide. Studies investigating the addition of chemotherapy to wide surgical margins and radiation have only shown moderate increases in DFI (8).

The newest proposed agent in the multi-modal approach to treating FISS is the use of immunotherapy in the form of interleukin-2 (IL-2) therapy. Two products studied in combination with surgical excision and brachytherapy (radioactive implants) – ALVAC® IL-2, a canarypox

virus vector expressing feline interleukin-2, and NYVAC® IL-2, a vaccinia virus vector expressing human IL-2— showed similar results although feline IL-2 is favored (4). The use of feline IL-2 prolonged median survival time to greater than 730 days when used in combination with surgery and radiotherapy. The rate of recurrence was also shown to decrease by 56% the first year and 65% after two years (4, 5). The use of a feline IL-2 product after surgical excision without the addition of radiotherapy or chemotherapy has not been evaluated (4, 9). In the US, a conditional USDA licensure has been granted for the product ONCEPT IL-2 which is a feline IL-2 canarypox vector product (ALVAC) approved for veterinary use in FISS in Europe. The use of this product has shown comparable results to the before mentioned ALVAC® product (13). ONCEPT IL-2 should be given in the pattern outlined by the manufacturer. The pattern determined for maximum effectiveness is four injections given at the corners of a 5 x 5 cm square with one injection in the center of the square (4).

As a cure for FISS has yet to be discovered, prevention is important in decreasing the occurrence. Prevention of FISS is centered around guidelines for vaccine administration. Vaccines administration to cats should be thought of as a medical procedure with medical necessity and legal stipulations considered (7, 8). Vaccines should be administered as low on the limb as possible with no vaccines and the fewest other subcutaneous injections as necessary injected in the intrascapular region. Injections should ideally be given with the needle directed toward the more distal portion of the limb to help facilitate an injection lower on the leg. The tail should be considered for use for vaccines due to the ease in amputation and likelihood of having clean surgical margins (7, 8, 14). Label instructions on vaccinations should be considered as newer guidelines suggest every three-year administration versus every year administration (7). For cats who have been diagnosed previously with FISS, necessity of vaccinations should be

considered as well as the benefit of going unvaccinated (7, 9). The use of non-adjuvanted vaccinations may decrease the rate of occurrence but FISS can still occur with these vaccinations (7, 9).

Conclusion

This case report describes the diagnosis and treatment of feline injection-site sarcomas in a cat. The treatments used on this patient, surgical excision and IL-2 alone, have limited literature to site its efficacy in treating feline injection-site sarcomas without the use of radiation therapy. The gold standard in diagnostics, an incisional biopsy, should reveal histopathologic findings of peripheral inflammation with lymphocytes and macrophages, granulation tissue, and multinucleated giant cells. Treatment is centered around surgical excision and other modalities including radiation, chemotherapy, and interluekon-2 treatments. Prevention is very important, and vaccinations should not be given to cats higher of the limbs, in the intrascapular area, or without medical necessity. Although a lot is known about feline injection-site sarcomas there is still not a known cure.

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