Kitty's Website

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Introduction

In 1991, an increase incidence of tumors developing at feline injection sites was first reported in the United States. These tumors were initially termed 'vaccine-associated sarcomas' and sparked both scientific and public attention. Later termed feline injection-site sarcomas (FISS), these neoplasms were found to be invasive sarcomas (mostly fibroscarcomas) that appeared to have characteristics that were distinct from other fibrosarcomas because they behaved more aggressively. Currently, FISS represent 6-12% of all feline tumors, and there is no definitive evidence that vaccines directly cause FISS. The most accepted theory suggests that a chronic inflammatory reaction at the site of the injection may cause some individuals to develop subsequent malignant transformation. Aggressive, radical excision is required to avoid tumor recurrence. For prevention, it is essential that clinicians avoid administration of any inflammatory inducing substances as frequently as possible. Vaccinations should be performed as often as necessary, but as infrequently as possible depending on a through risk assessment.[1, 12]

History and Case Presentation

Kitty Webber, an approximately 11-year-old domestic longhair, presented to MSU CVM oncology service on February 30, 2019. She was referred for a tumor on her left side, as well as vomiting and weight loss. It was reported that Kitty was an indoor only cat that lived with three dogs. Kitty's tumor had been progressively growing since it was first discovered a few months prior. Kitty's owners described that she had a history of vomiting, but she continued to eat normally. It was stated that her last vaccines were given in 2015.

At the time of presentation, Kitty was quiet, alert, and responsive. She had a heart rate of 168 beats per minute, a respiratory rate of 40 breaths per minute, and her temperature was 99.4

degrees Fahrenheit. She had a thin body condition score of 3/9, with 5 being ideal. She had a slight skin tent and her mucous membranes were pink and moist. Her heart and lungs auscultated normally. She had a firm, lobulated mass on her left body wall with areas of fluctuant pockets. The mass measured 5.6 x 7.28 x 4.76 cm. Her abdomen was non-painful on palpation. The rest of her physical examination was unremarkable.

Diagnostic Approach/Considerations

On January 30, complete blood count, serum chemistry, blood gas analysis, urinalysis, urine culture, total T4, thoracic radiographs, renal panel, abdominal contrast and computed tomography, and cytology of a fine needle aspirate of the mass were performed. Complete blood count revealed a mild anemia with a hematocrit of 29.6% (30.0-46.0) and a mild neutrophilia of 17100/ul (2500-12800). Serum chemistry revealed a mild azotemia with a blood urea nitrogen of 54mg/dl (10-40) and creatinine of 2.09mg/dl (0.40-2.00). A moderate hypercalcemia was also detected at 13.4mg/dl (8.2-10.6). A blood gas revealed a moderately elevated ionized calcium at 1.62mmol/L (1.20-1.32).

Thoracic radiographs revealed a large (measuring approximately 6.7 x 5.8 x 5.9 cm), smoothly marginated, lobulated, soft tissue opaque mass along the left lateral thoracic body wall. A pathologic fracture was discovered at the level of the 11^{th} rib. Abdominal contrast enhanced computerized tomography revealed a large (approximately 6 x 6.1 x 9.8 cm), irregularly shaped, irregularly marginated, heterogeneous, soft tissue dense mass with significant heterogeneous contrast enhancement. It was noted that there were numerous variable shaped, variably sized, smoothly marginated, rim contrast enhancing fluid dense pockets present, with the largest measuring 6 x 3.8 x 5.6 cm. The mass was described to be significantly disrupting the normal

contour of the abdominal body wall and extending lateral in a convex manner. The mass was also noted to be causing concave displacement of the body wall medially which also displaced the stomach and liver. Both kidneys were described to be irregularly marginated with heterogeneous regions of reduced contrast enhancement within the cortex.

Cytology of the mass revealed moderate to high numbers of spindle cells that were forming clusters. These cells had basophilic cytoplasm and oval to elongated nuclei. Anisocytosis and anisokaryosis were noted to be mild to moderate. The nucleus to cytoplasm ratio was described to be moderate and the chromatin was coarse with some of the cells having one or two small prominent nucleoli. There was a large spindle cell population with mild to moderate atypia. The sample appeared to have a high cellular density with a minimal amount of matrix.

All other diagnostic findings were within normal limits. Using the information from the diagnostics stated above, Kitty was presumptively diagnosed with feline-injection site sarcoma. She was also diagnosed with chronic kidney disease, hypercalcemia of unknown origin, normochromic normocytic anemia, and loss of body condition.

On February 4, Kitty was admitted to the MSU-CVM intensive care unit to correct her azotemia with intravenous fluid replacement. On February 6, Kitty was anesthetized for a mass excision and thoracic wall resection. An elliptical incision, approximately 25 cm in length, was made around the mass on the left lateral thorax. A combination of blunt dissection, sharp dissection and monopolar electrocautery was used to dissect through the subcutaneous tissue and fat. Hemostasis was maintained with monopolar electrocautery. A partial lung lobectomy of the left caudal lung lobe was performed as it was confluent with the mass. Ribs 10-13 were also removed because they were confluent with the mass. Reconstruction of the caudal thoracic wall

using the technique of diaphragmatic advancement was performed. For additional closure of the defect, a latissimus dorsi muscle flap was utilized. An approximately 2cm by 2cm piece of Porcine Small Intestinal Submucosa was used to cover what could not be covered with autogenous grafting. The skin around the rest of the defect was undermined using blunt dissection to relieve tension, and towel clamps were used to pull the skin edges together. The subcutaneous tissue and skin were closed with a continuous pattern and cruciate pattern, respectively. An esophagostomy feeding tube was placed to maintain adequate nutrition after surgery. The mass was submitted for histopathology which revealed a cell population that was highly consistent with a post-vaccine associated sarcoma. Lateral margins appeared to be completely excised and there was no neoplastic tissue within 1-2 mm of the deep margin.

Pathophysiology of FISS

Investigation into the pathophysiology of the development of FISS produced the singular predominant theory that these tumors are induced secondary to a chronic and immense inflammatory response to a vaccine or injection. This inflammation is suggested to ultimately cause malignant transformation of surrounding fibroblasts and myofibroblasts. The theory is supported by the characteristic histologic appearance of feline injection site sarcomas, which includes the presence of increased numbers of inflammatory cells (predominantly lymphocytes), multinucleated giant cells, central areas of necrosis, and in some cases, a grayish-blue material within macrophages, consistent with aluminum-based vaccine adjuvant. Adjuvanted vaccines are also frequently identified in the histological or ultrastructural findings of these sarcomas, indicating a strong causal association.[2]

Initially, only the rabies and FeLV vaccines were identified as risk factors, but subsequently other vaccines including feline panleukopenia virus (FPV), feline herpesvirus-1 (FHV-1) and feline calicivirus (FCV), were also found to be associated with the development of these neoplasms.[3] Additionally, injections such as long-acting glucocorticoids, penicillin, and meloxicam have been linked to sarcoma formation.[1] Fibrosarcomas have also been reported at the sites of deep, non-absorbable sutures, microchip implantation, and around a surgical sponge that was left in the abdomen.[4,5,6] However, the risk appears to be the highest with adjuvanted vaccines.[7] Consequently, it can be concluded that any substance that causes long lasting inflammation can induce an injection site sarcoma.

It is theorized that the degree of a cat's individual inflammatory response also plays a role. It has been reported that there is a higher incidence of feline injection site sarcomas in sibling cats, and that some cats tend to develop more than one feline injection site sarcoma. It is thought that growth factors promote proliferation, induce malignant transformation, and are involved in the regulation of angiogenesis. Overexpression of growth factors and oncogene activation has been displayed in cats with FISS and is thought to contribute to tumor development. [1,8]

Treatments and Prognosis

Aggressive, radical, surgical excision is essential to avoiding tumor recurrence. This can be achieved by utilizing contrast enhanced computerized tomography or magnetic resonance imaging to determine the extent of the tumor. This is essential because it has been shown that the actual size of tumors determined by computerized tomography can be up to twice the size estimated by physical examination.[9] Surgeons should aim to achieve complete surgical resection

with 5cm margins and one facial plane underlying the tumor. Incomplete resection can result in recurrence as early as two weeks after the surgery.[1] With tumor free margins and radiation therapy, patients were reported to have a disease-free interval of 700 days. With incomplete margins and radiation therapy, the disease-free interval was only 112 days. However, even with complete, disease free margins and radiation therapy, up to 50% of feline injection site sarcomas reoccurred. Up to 70% of feline injection site sarcomas occurred with disease free margins and no radiation therapy.[11]

Chemotherapy remains an option for palliative treatment in cats who are not appropriate surgical candidates.[11] However, immunotherapy may become a promising option for future treatment. Recombinant feline IL-2 is currently available in Europe for the treatment of FISS in combination with excision and radiation therapy. In a randomized controlled clinical trial, IL-2 treatment resulted in a significant longer time to relapse (730 days) than in the reference treatment group (287 days), and a significant reduction of the risk of relapse by 56% at one year and 65% at two years.[12]

Prevention

One to 4 out of 10,000 vaccinated cats in the United States will develop FISS.[9] Because of the aggressive nature of this neoplasm and the relatively poor prognosis, prevention is critical. Injections in cats should only be given at sites where surgery would likely lead to a complete cure (distal limb, tail, lateral abdominal skin).[1,14] Furthermore, avoiding the administration of irritating substances to reduce the number of inflammatory reactions is crucial. Vaccination should only occur as often as necessary. Three-year vaccinations are preferred and a through risk assessment should be used to determine if feline patients need FeLV vaccinations. Post vaccine

monitoring should also play an important role. Practitioners and owners should follow the "3-2-1"-rule. Further diagnostics are warranted if the mass is still present three months after vaccination, if the mass becomes larger than two cm in diameter, or if the mass is increasing in size one month after vaccination. Furthermore, intramuscular injections should be avoided because they are more difficult to detect early. Oral and intravenous options should be considered preferable to intramuscular or subcutaneous injections.[10] Factors such as size of the needle, syringe, or velocity of the injection did not play a role in the development of FISS. However, practitioners should avoid giving cold vaccines, because there is higher risk of FISS development from cold vaccines than vaccines that were given at room temperature.[13]

Case Outcome

After the mass excision and thoracic wall resection were performed, Kitty's recovery from anesthesia was abnormal. On physical exam she was recumbent, with a temperature of 96.1, a heart rate of 214, and respiratory rate of 35 breaths per minute. Her pulse quality was fair, and her mucus membranes were pale with a capillary refill time of greater than two seconds.

Kitty had an SPO2 of 85%, which was most likely related to her lung lobectomy. Both handling the lung tissue and the removal of her left caudal lung lobe most likely caused decreased ventilation to her alveoli (V/Q mismatch), resulting in hypoxemia. Kitty's decreased lung capacity was managed by placing her in a cage with 60% oxygen.

Kitty had a systolic blood pressure of 50mm/Hg, which was mostly likely caused by the blood loss associated with the aggressive mass resection. She was treated with intravenous fluid therapy and Hetastarch to increase blood volume. Norepinephrine was utilized to increase blood

pressure by stimulating constriction of her blood vessels. Her pain was well controlled with a fentanyl CRI.

Kitty had normocytic, normochromic anemia (PCV 19%, TP 5.8) upon recovery. This abnormality was mostly likely related to both her chronic kidney disease and blood loss from the surgical resection of the mass. An Eldon Blood Typing Kit determined that she was blood type A. She was crossed matched with six different donors before a compatible match was found, indicating she had strong immune response to a multitude of type A red blood cells. She was given 60mL of whole blood over 6 hours without complications.

The following morning (February 7), Kitty was bright, alert, and responsive. Her anemia was corrected (PCV 21.3, 8.4) and systolic her blood pressure was normalized at 120mm/Hg via doppler blood pressure. Her SPO2 returned to normal limits at 98%. Intravenous norepinephrine and fentanyl were discontinued, and oral buprenorphine was instituted for pain control. The following day (February 8), Kitty was removed from 60% oxygen and all remaining intravenous medications were discontinued. Kitty continued to be monitored in surgery wards for six days. The esophagostomy tube that was placed during surgery was never utilized because Kitty began eating, drinking, urinating, and defecating promptly.

Kitty was discharged on February 10, with instructions to return to the MSU-CVM oncology for an incision recheck and to discuss further treatment options. She was discharged with oral buprenorphine for pain control. On February 28, Kitty's owners described that she was doing very well at home. On physical exam mild tissue swelling was noted at the esophagostomy site and the incision from the mass removal appeared to be healing appropriately. The esophagostomy tube was removed, and instructions were given to return on March 4 to recheck

blood chemistry and perform contrast computerized tomography to plan radiation therapy. However, Kitty did not return for further treatment and was lost to follow up.

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