



Update on Vaccine Associated Sarcomas in Cats

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Background: An association between vaccination and soft tissue sarcoma formation was first reported in the early 1990's. Since that time information about this phenomenon has grown exponentially. The true etiology of Vaccine Associated Sarcomas (VAS) remains unknown. Initial investigations revolved around adjuvanted vaccines, especially those containing metals (aluminum). Further investigation has revealed that VAS may occur without adjuvant products. Other variables that have been considered are needle gauge, syringe reuse, temperature of vaccine, shaking of vaccines and massage of the injection site. Although the exact relationship between the vaccination and the formation of VAS is unclear, it is apparent that cats may have an inappropriate or overzealous inflammatory or immune reaction to components at vaccine sites. The reaction leads to uncontrolled proliferation of fibroblasts and myofibroblasts that in some cases undergo metaplastic or neoplastic transformation.

Growth factors are essential for regulation of the cellular events that lead to wound healing. These factors, when added to fibroblast cultures, have also been associated with neoplastic changes. Many oncogenes cause cancer by coding for and causing overexpression of growth factors and their receptors. VAS have been found to have immunoreactivity to Platelet Derived Growth Factor(PDGF) and its receptor, Epidermal growth factor EGF and its receptor and Transforming growth factor-beta(TGF- β), while non-VAS do not. Research in this field is ongoing.

Many studies have also been performed to evaluate viruses as an inciting factor. The presence FeLV, Feline Sarcoma virus, polyomavirus, FIV, and papillomavirus has not been demonstrated.

Incidence of VAS is estimated to be between 1/1000-1/10,000. Cats are generally presented for a palpable mass in or near the injection site. The timing of the occurrence of VAS following vaccination is highly variable. Tumors have been reported 2 months to 10 years after vaccination. Most masses evaluated prior to 3 months are histologically consistent with granuloma.

Patient evaluation: Any mass located in a vaccination site that persists more than 3 months should be surgically excised. Preoperative biopsy is an important first step. When performing a biopsy it is important to remember that the entire biopsy tract must be removed at the definitive surgery. Fine needle aspiration is less reliable as sarcomas generally do not exfoliate well. Incisional biopsy is best performed with Tru-Cut type

instruments. Open, blade incisional biopsy procedures risk more bleeding and tumor seeding thus increasing the size of the definitive surgical field.

Imaging: Preoperative thoracic radiographs are indicated with VAS. The incidence of thoracic metastasis may be as high as 22%. Tumor imaging should be performed when ever possible. Contrast-enhanced computed tomography (CT) or MRI are the modalities of choice. A recent study by McEntee demonstrated that the volume of a tumor based on the contrasted-enhanced CT images was on average twice the size of the tumor based on physical exam (caliper measurements). Even tumors that feel relatively small and not fixed to underlying tissues have been shown to have deeper attachments.

Generally MRI provides better soft tissue detail than CT scan. A post gadolinium contrast, T2 weighted image has shown high sensitivity for tumor extensions and is the imaging technique of choice at the Veterinary Specialty Hospital.

Treatment:

Surgery: Early, aggressive surgery represents the best chance for a cure. There are mixed results in the veterinary literature regarding the response and recurrence rates with surgery alone. Hershey AE, et al evaluated the prognosis VAS following surgery in 61 cases. The median time to first recurrence (TFR) was 274 days for tumors removed at referral institutions and 66 days for tumors removed by a referring veterinarian. Radical excision resulted in much longer TFR (325 days) than did marginal excision (79 days). The need for aggressive procedures is clear. Surgery often requires partial scapulectomy, resection of dorsal spinous process, amputation, hemipelvectomy and thoracic or abdominal wall reconstruction. The accepted standard of 2-3cm lateral margins and one fascial plane deep will generally result in clean microscopic margins, but an unacceptable rate of recurrence. Overall (national) recurrence following surgery alone is estimated to be 50% at 1 year following surgery alone. Kuntz CA described a modified wide local excision of VAS in cats that includes 3-5cm lateral and 2 planes deep to the mass. This aggressive resection may improve recurrence rates to less than 5%.

General oncologic surgery principles apply. The entire specimen should be submitted for histologic examination. The specimen should be properly marked and oriented before submission. A variety of methods can be used to mark the tumor margins, including placement of suture tags and the use of marking dyes or ink. Additionally, hemoclips should be placed at surgery to mark the margins of excision in the event of future radioation therapy.

Radiation/Chemotherapy: Due to the high rate of local recurrence, radiation has been implemented as either primary or adjuvant therapy of VAS. Cats generally tolerate radiation better than dogs. Presently recommended doses are in the low 60 Gy range. Use of electron therapy (vs photon) can be beneficial in that electrons are more superficially penetrating and will often spare deeper tissues. There is disagreement as to whether to perform pre or post-operative radiation. The benefit of preoperative radiation is that surgery disturbs the tissues and results in a larger radiation field. Surgery may also create hypoxic areas that are resistant to radiation. Preoperative radiation may result in a less radical surgery. The problem with preoperative radiation is related to the tissue

changes encountered. Irradiated tissues are compromised and are less resistant to tension and infection. I currently recommend radiation therapy in the post operative setting.

Treatment with a combination of doxorubicin, surgery, and radiation versus surgery and radiation alone for VAS was recently evaluated at Colorado State University. 25 cats were treated with one of the two protocols. TFR was 661 days for surgery, doxorubicin and radiation. TFR has not yet been determined for the surgery and radiation alone. Median survival was 674 for doxorubicin, surgery, and radiation and 842 for surgery and radiation alone. This study did not determine significant differences from the two groups. If this study is compared to the study by Hershey et al, looking at surgery alone, it appears that adjuvant therapy may prolong both TFR and median survival. The efficacy of the addition of doxorubicin is uncertain.

Chemotherapy: Several agents, including carboplatin, doxorubicin, mitoxantrone, cyclophosphamide and vincristine have been used with VAS. Some partial and some complete remissions have resulted, however, chemotherapy alone should not be considered for definitive therapy. Barber et al from the University of Pennsylvania reported on twelve cats with “non-resectable” VAS that received doxorubicin (20 to 30 mg/m², intravenously) on day one and cyclophosphamide (50 mg per cat, per os) on days three and five or divided into four daily doses over days three to six. The cycle was repeated every 21 days. A partial response was seen in 50% of the cases and 4/12 cases became surgical candidates.

Summary and Recommendations:

The Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) current guidelines: The task force prepared concise guidelines to assist practitioners in diagnosing and managing vaccine-associated sarcomas. The following recommendations are based on information available as of April 1999 and are subject to revision as new information becomes available.

Diagnosis:

1. Record anatomic location, shape, and size (measured by caliper and recorded in three dimensions) of all masses that occur at the site of an injection.
2. Manage a mass that develops at a previous injection site as if it were malignant until proven otherwise. A lesion should be fully assessed and aggressively treated if it meets any one of the following criteria: Persists more than 3 months post-injection; Is larger than 2 cm in diameter; Is increasing in size after one month post-injection.
3. If a mass meets one or more of the above criteria, we recommend that you perform a diagnostic biopsy prior to surgical excision. A tru-cut needle biopsy or incisional wedge biopsy is preferred for diagnosing lesions. Fine needle aspiration cytology is considered unreliable for the diagnosis of VAFS and is not recommended.

Management - Masses confirmed as malignant should be handled as listed below:

1. Perform routine thoracic radiographs and pre-operative labwork for any malignant mass.

2. When feasible, histologically confirmed VAFSs should be imaged by computerized tomography (CT) or magnetic resonance imaging (MRI).
3. Consult with an oncologist for current treatment options, prior to initiating therapy.
4. Never "shell out" a sarcoma. Incomplete surgical removal of a sarcoma is the most common cause of treatment failure. Employ oncologic surgical techniques to avoid seeding malignant cells. Remove at least a 2-cm margin in all planes, including the deep side.
5. Submit the entire excised specimen for histopathology. Mark the excised mass with India ink or suture tags to provide an anatomical reference to facilitate subsequent treatment.
6. Report all histologically confirmed VAFSs to the manufacturer and to U.S. Pharmacopoeia Veterinary Practitioners' Reporting Program.
To make a report or request reporting forms, call 8004-USP-PRN (800-487-7776) or visit the USP Web site at www.usp.org.

After a sarcoma has been removed:

1. Recheck by physical examination monthly for the first three months, then at least every 3 months for one year.
2. Perform additional diagnostic procedures as appropriate for the abnormalities detected.

References:

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3. Dernell WS Vaccine Associated Sarcomas in cats. In *Proceedings of the ACVS Symposium, Chicago, IL 2001* pg 186-190
4. Barber LG et al. Combined doxorubicine and cyclophosphamide chemotherapy for nonresectable feline fibrosarcoma. *J Am Anima Hosp Assoc* 2000;36:416-412