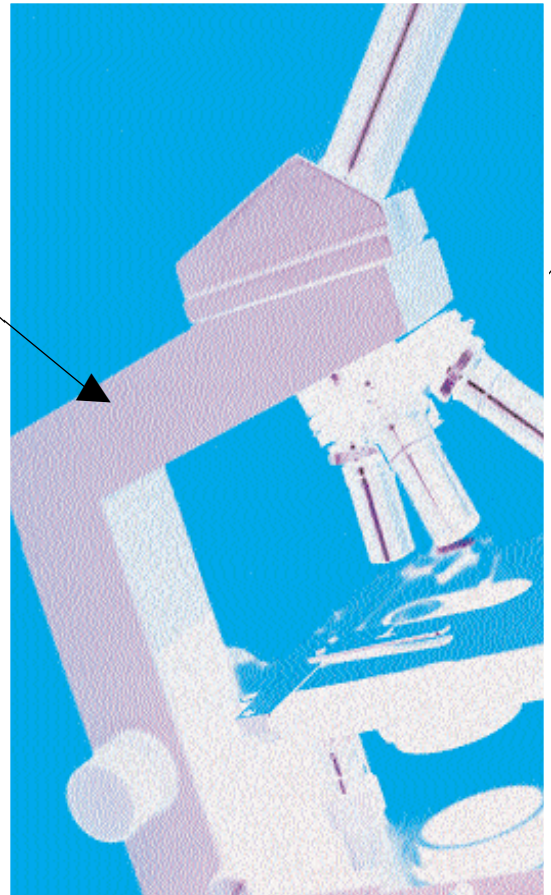


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eline vaccine-associated sarcomas were initially recognized in the late 1980's. An increase in fibrosarcomas was noticed in the pathology Laboratory of Pathology at the University of Pennsylvania School of Veterinary Medicine. This increase coincided with the implementation of a mandatory feline rabies vaccination law. The sarcomas had similar histologic features to injection site inflammatory reactions. Later research revealed aluminum, a common vaccine adjuvant, within the cytoplasm of tumor macrophages. This increased suspicion that vaccine was more than just circumstantially involved.

A letter to the editor<sup>1</sup> of the Journal of the American Veterinary Medical Association (JAVMA) in 1991, was the first warning made to the general veterinary profession. The letter reviewed the increase in sarcomas at vaccination sites and the fact that the increase



## Feline Vaccine-Associated Sarcomas: Historical Review & Current Recommendations

appeared to be correlated with the enactment of the 1987 Pennsylvania state law requiring rabies vaccination of cats. The letter shared the anecdotal information that veterinarians noted that some of the fibrosarcomas arose from vaccination sites shortly after injection and that some of the fibrosarcomas developed in an area that had previously been excised and diagnosed histologically as injection site reactions. Practitioners were encouraged to keep explicit records regarding date and anatomical location of vaccine administration. They were also directed to submit suspected masses for histologic examination. Prompted by the letter, Kass et al performed a retrospective study<sup>2</sup> of 345 cats in Hawaii and California and confirmed causal and temporal relations between vaccination and sarcoma development. They not only found that vaccination for feline leukemia virus (FeLV) and rabies virus were related to sarcoma development, but also that the reaction to vaccines was additive. In other words, the likelihood of development of sarcomas increased as the number of vaccines given simultaneously at a particular site increased. A retrospective study comparing vaccination site and nonvaccination site fibrosarcomas<sup>3</sup> revealed that sarcomas at vaccine sites were larger and seen in younger cats. Vaccination site fibrosarcomas also had a higher rate of recurrence. A prospective study followed about 2,000 cats with FeLV, FVRPC and rabies vaccines injected at separate sites. Within a few years, five post-vaccinal sarcomas arose and they were all at rabies vaccine sites. The conclusions gleaned from these studies were that, a) the sarcoma rate was not influenced by brand of vaccine, b) both adjuvanted and non-adjuvanted vaccines were incriminated, c) there was no sex predilec-

tion, and d) there was no evidence of concurrent feline vaccine-associated sarcomas and infection with FeLV or feline immunosuppressive virus (FIV). The recommendations at that time were to vaccinate at separate sites and to keep complete records regarding vaccine administration.

The press reaction was mixed as the feline vaccine-associated sarcoma story unfolded in veterinary journals, human medical journals and all manner of lay publications.

The response by the veterinary profession germinated in August 1996 when the California Veterinary Medical Association gathered experts from around the country to discuss the issue and make recommendations. This effort grew and eventually the American Veterinary Medical Association, American Animal Hospital Association, American Association of Feline Practitioners and the Veterinary Cancer Society formed the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF), which met in November 1996. Its members included representatives from these organizations. They came together with a common pursuit. The VAFSTF goals were to "facilitate investigation of the epidemiology, etiopathogenesis, treatment and prevention of these malignancies, as well as to disseminate information to veterinarians and the cat-owning public."

The VAFSTF published the initial vaccination guidelines and also published a guide to the diagnosis and management of suspected sarcomas. This information was mailed out to veterinarians in an effort to standardize the veterinary profession's response to this emerging issue. Their Web site (<http://www.avma.org/vafstf/>)<sup>4</sup> provided another method to disseminate this and other information. They have funded many studies over the years

with the support of the founding organizations and various pharmaceutical companies, including Fort Dodge Animal Health. The effort put forth since 1996 has provided much-needed information.

The etiology of feline vaccine-associated sarcomas remains primarily linked to administration of FeLV and rabies vaccines. There have been a few reports indicating injection of antibiotics, SQ fluids, long-acting corticosteroids or lufenuron could have caused injection-site sarcomas, but it is challenging to evaluate some of these studies because of difficulty proving that a vaccine wasn't previously given to the cat at the site of the sarcoma. Vaccine injection remains the most common association by far. The predominant theory of sarcoma pathogenesis, that persistent inflammation or wound healing associated with vaccine components leads to proliferation of fibroblasts and myofibroblasts that undergo neoplastic transformation through unknown mechanisms, has remained essentially unchanged.

Many feline vaccine-associated sarcomas' mechanisms have been postulated and investigated. Platelet-derived growth factor (PDGF) released from platelets, macrophages and smooth muscle cells, stimulates fibroblast proliferation. PDGF and other growth factors can play a role in tumorigenesis. Cells that produce growth factor may also make the receptor for the growth factor. This process forms an autonomous loop, continuously turning itself on so that affected cells do not stop dividing, hence leading to neoplasia. Overexpression of PDGF and its receptor have been shown via immunohistochemistry on paraffin-embedded blocks of feline sarcomas and in feline sarcoma cells

in culture. A compound that blocks the PDGF receptor, when applied to sarcoma cell cultures, inhibited their growth. This line of research has the potential to be important in terms of sarcoma prevention and treatment.

There are several exciting areas of study that involve genetics. Research involving the p53 gene shows promise. Many clients will be aware of the p53 gene; it even made the cover of Time Magazine. The presence of fully functional p53 genes somehow prevents cancer, although precisely how this prevention occurs is still being researched and is not fully understood. Alterations or mutations to this gene are important in tumor genesis. Research has proven that compared to normal tissues, cancer tissues produce higher levels of mutant p53 protein. The role this plays in pathogenesis is, again, poorly understood, but one study showed that cats with cytoplasmic expression of p53 had a shorter time to local tumor recurrence than cats with nuclear expression of p53. There is potential for p53 to be used as a prognostic indicator.

One hypothesis being studied is that there is something different about the cats that develop feline vaccine-associated sarcomas. After all, the vast majority of vaccinated cats do not develop tumors, so maybe there is something genetically different about those that do. Genetic predisposition research is ongoing and may be helpful. There are also some studies investigating genes that are differentially expressed during tumor development. There is hope that this research could lead to a genetic marker to identify cats that are prone to the generation of feline vaccine-associated sarcomas.

In addition, there have been recent studies addressing the mutagenicity of vaccines. The develop-

ment of the AL assay has been important in this area because it evaluates the toxicity and mutagenicity of vaccine products. Some of these research studies found that adjuvanted vaccines were more toxic and mutagenic than nonadjuvanted vaccines, but the research is continuing at this time, and what it means as far as prevention and management of feline vaccine-associated sarcomas is unknown.

The question of whether FeLV or FIV are involved has been researched by Dr. John Ellis's laboratory. He and his group found no molecular or immunohistochemical evidence of either of those two viruses playing a role in feline vaccine-associated sarcoma development. They also investigated papilloma and polyomavirus and found no connection. It does not appear that there is any viral component to the pathogenesis of these tumors.

Diagnostic techniques have improved since 1996. Incisional biopsy is now the method of choice vs. excisional. A positive feline vaccine-associated sarcoma diagnosis requires such a wide margin of excision that it is best to confirm the diagnosis first to free the surgeon to go after them very aggressively, because these tumors are uniformly prone to local recurrence. Grading them is unimportant. They are all infiltrative, aggressive tumors. Shelling them out will always be insufficient. Using computerized tomography (CT) or other advanced imaging techniques like magnetic resonance

imaging (MRI) is the best way to diagnose the extent of these tumors. So starting with a wedge biopsy to get the diagnosis, following with advanced imaging to determine the margins and aggressive surgery to remove the entire mass is the treatment plan advised today.

Pre- and post-treatment high dose radiation can extend time to local recurrence, but some papers suggest it may increase metastasis. There are current studies evaluating the radiosensitivity of cultured sarcoma cells and investigating biological markers which might be used to indicate which cats would benefit from radiation and which would not. Chemotherapy is a palliative therapy at best. Doxorubicin and carboplatin are the most commonly used.

In conclusion, until an effective treatment is discovered, prevention and management are the keys. One of VAFSTF's first recommendations still holds true. Vaccination is a medical procedure and should be individualized to the individual patient.



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4. <http://www.avma.org/vafstf/> contains a complete list of references recommended by the task force.