Feline Vaccine-Associated Sarcoma

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I. Introduction

It has been more than 20 years since Dr. Mattie Hendrick, a veterinary pathologist at the University of Pennsylvania, published her article titled "Postvaccinal sarcomas in the cat: Epidemiology and electron probe microanalytical identification of aluminum" in *Cancer Research*, first linking vaccination to sarcoma development (1). Dr. Hendrick initially brought her concerns to the forefront in 1991 in a letter to the editor of the Journal of the American Veterinary Association where they suggested a rise in sarcomas at vaccines sites may be associated with the recent enactment of a state law in Pennsylvannia requiring the rabies vaccination of cats. During the same time period of the study (1985) there was the introduction of the first Feline Leukemia vaccine which contained aluminum adjuvant and the switch from a modified live rabies vaccine to an adjuvanted killed rabies vaccine. Since then, many of Dr. Hendrick's observations, and the studies and findings of other researchers, have matured and solidified our understanding of the etiology, the risk factors, and the incidence of vaccine-associated sarcomas in cats. Although our understanding of this condition is still incomplete I will present an overview of the current findings related to feline vaccine-associated sarcomas, their pathogenesis, and their clinical management.

II. Sarcoma Development

The association between sites of vaccine administration and subsequent development of high-grade sarcomas and other mesenchymal tumors in cats has been well documented and accepted by the veterinary community (1-7). The association between previous vaccination and tumor development at vaccination sites in cats has been observed worldwide and has been reported to have a prevalence ranging from 1 in 1000 to 1 in 10,000 in cats (4,10,19,20,39) and its has been estimated that up to 22,000 new cases of vaccine associated sarcomas develop annually (31). Vaccine site tumors have also been reported in dogs, horses, and ferrets but less frequently (32, 36, 46). The time from vaccination to tumor development may be as little as 3 months, with 93% developing within four years (39). Sarcoma development has also been reported sporadically at the site of injection or implantation of other substances including; lufenuron, long acting penicillin, long acting corticosteroid preparations, meloxicam, and implanted foreign material such as suture and microchips (27,6,23,24). Tumorigenesis associated with chronic inflammation is well document in a variety of species and appears to correlate with the amount of inflammation and the degree of fibrous proliferation associated with the foreign materials (43,44). This is consistent with the hypothesis that chronic inflammation associated with adjuvant most often included in rabies and feline leukemia virus vaccines may play a role in the development of vaccine associated sarcomas (9). A 2002 report from the United Kingdom found that injection site sarcomas were five times more likely to develop in cats that received aluminum adjuvanted feline leukemia vaccines than non-adjuvanted vaccines (13). Further supporting the role of adjuvanted vaccines in the development of sarcoma, was a recent study by Stephen Shaw et al 2009. In that study, the change in the location of vaccine associated sarcomas from 1990-2006 was studied. In 1996, there was a recommendation to change the site of administration of the most frequently administered adjuvanted vaccines, rabies and leukemia, from the intrascapular space to the rear legs. Since this recommendation has been made, a drop in sarcomas developing in the intrascapular space was noted along with a more than doubling of sarcomas being reported in the rear legs being observed (38).

The initial reports identified only FeLV and rabies vaccines with an increased risk for sarcoma development at site of vaccination. An additional study from Canada (Lester et al) suggested a role for other killed adjuvanted vaccines, including panleukopenia and respiratory viruses, in tumors developing in cats that had not received FeLV vaccination. The incidence of sarcomas in this population decreased after switching to modified live virus vaccines (19). Although tumors have been reported to develop subsequent to the administration of non-adjuvanted vaccines, it is thought to be less common and may be associated with other factors such as

trauma (10). Trauma associated with the injection process, including muscle tearing or the introduction of hair into the subcutaneous tissues at the time of injection, can result in inflammation (11). Although vaccines commonly contain aluminum hydroxide in suspension as an adjuvant, post vaccinal inflammation and sarcoma development appear similarly with soluble adjuvanted (carbopol) vaccines (11). In light of these observations, injection-site sarcomas (ISS) may be a more accurate descriptive term for these tumors. It is clear that not all substances carry the same risk, and reports of sarcoma initiation following insulin or Droncit administration in cats are lacking. It is thought that the risk of tumor development may relate to the reactive nature of the vaccine components or other injectable, as well as the qualitative nature of the local inflammatory response and the various oxidative products produced by the cellular response. This is in addition to the magnitude of the fibrous response to the vaccine and it components. Dr. Elizabeth McNiel at the University of Minnesota is investigating the role of free radical damage associated with feline vaccines in producing mutations that may stimulate oncogenesis. She found that cell cultures exposed to adjuvant-containing vaccines developed mutations in a concentration-dependent manner, while no mutations were found after exposure to non adjuvanted vaccines (34). She further found that the mutations could be blocked by a free radical scavenger (34). The World Health Organization International Agency for Research on Cancer in 1999 has acknowledged the evidence of potential carcinogenicity of feline adjuvanted vaccines (12). Although not all veterinarians are convinced of the role of inflammation in the pathogenesis of vaccine-associated sarcomas, chronic inflammation is a well known tumor promoter in a variety of species. The cat as a species is uniquely sensitive in this regard, frequently developing mesenchymal tumors secondary to chronic inflammation associated with ocular injury and more so than any other species(26). Genetic susceptibility to foreign body inflammation induced tumorigenesis is not unique to the cat and has also been studied in mice where some strains of mice are known to be resistant to foreign body sarcoma development while other strains can be highly susceptible.

Other potential causes of tumors such as viruses have also been studied. Research performed by Dr. Ellis *et* al appears to rule out the potential role of viral agents, including FIV, FELV, papillomavirus, and polyomavirus, in the etiology of this disease in cats (14,15,16,25). Genetic factors are often considered when cancers occur in younger animal such as vaccine associated sarcomas. The cat is more susceptible to oxidative injury ie heinz body formation, acetomenophen toxicity, and steatites, than other species. This characteristic may be important in tumor initiation. At the University of Minnesota, Dr. Sagarika Kanjilal and her colleagues studied the role of genetic predisposition in the development of vaccine associated sarcomas. Normal P53 is up regulated in the presence of DNA damage and suppresses tumor cell growth. Alterations in P53 were found in some cats with vaccine associated sarcomas. P53 mutations have been associated with initiation and progression of tumors in a variety of species.

III. Histologic Features

Tumors that arise at sites of previous vaccination are similar to those observed arising from areas of chronic inflammation in other species and are mesenchymal in origin: osteosarcoma, chondrosarcoma, fibrosarcoma, malignant histiocytoma, giant cell tumor, rhabdomysarcoma, and leiomyosarcoma being reported. However fibrosarcoma account for 80% of the tumor types observed at sites of vaccination (37). This observation suggests a local pluripotential mesenchlymal cell as the target for the malignant transformation.

In addition to recent immunohistologic and ultra structural descriptions of vaccine-associated sarcomas, good microscopic descriptions have provided pathologists with a better capability to identify these lesions (17). The characteristics of intratumoral lymphoplasmacytic inflammation, giant cells, intracellular basophilic material and myofibroblastic differentiation have helped diagnostic pathologists in identifying these lesions. Of clinical significance, and a potential reason for frequent surgical failure in the management of VAS, is the finding that histologically normal looking cells up to five centimeters from the tumor have up regulated P53 and are indications of DNA damage and a potentially premalignant state and risk for later treatment failure, a phenomenon known as field carcinogenesis(33).

IV.Clinical management

Post vaccinal sarcomas are typically diagnosed in younger cats versus sarcomas at non vaccine sites and are usually presented within four years of vaccination although some have been reported up to ten years after vaccination. Post vaccination lumps are very common, especially

after the administration of rabies and FeLV vaccines that are commonly adjuvanted. The majority of these lumps will take a benign course and resolve within three months. The task force guidelines will help the veterinarian in the management of these lumps. If a lump develops at the vaccine site or within five centimeters of the vaccine site follow the THREE, TWO, ONE rule: A biopsy of the mass should be done if the mass has persisted for more than three months, is greater than 2 cm in diameter, or is increasing in size one month after injection (35). The degree of inflammation associated with these tumors makes cytologic evaluation unreliable thus a core biopsy should be taken. Simple lumpectomy is not recommended in that if it is proven to be a tumor, wider surgical margins are required to get both the tumor and premalignant tissues. There are no recognized histopathologic prognostic indicators for vaccine associated tumors but most have a short tumor doubling time, and 86% of recurrences develop within six months (45). After tumors have been confirmed, clinical stage is desired prior to surgery. Three view chest radiographs are recommend, but contrast-enhanced CT imaging when available can improve surgical planning and is superior to routine radiographic evaluation in detecting pulmonary metastasis (40). The most common site of metastasis are the lungs , followed by the lymph nodes and other internal organs The clinically detectable metastatic rate at the time of diagnosis is 5% and the reported rate of metastasis is 0-28% (40). Surgical management as the sole modality of treatment is generally inadequate as there is 30-70% local recurrence depending on tumor margins, but it is considered the most important component in a multimodal treatment regimen. Surgery should be aggressive and should include the recognizable tumor and the margins should be 3-5 cm and two muscle planes deep. Despite aggressive surgical intervention and histopathologic reports indicating no tumor cells observed at the surgical margins there is a 50% recurrence rate (45). The recommendation to give rabies and FeLV vaccines in the rears legs are in part based on the better survival in patients that develop sarcoma on the rear legs and undergo amputation. Radiation therapy alone can be palliative but is seldom curative. It has been shown to significantly prolong survival in patients when combined with surgery in a number of studies. The use of chemotherapy in the management of vaccine associated sarcomas has been shown to have limited value. Drugs with activity against vaccine associated tumors include carboplatin, vincristine, mitoxantrone, doxorubicin, and cyclophosphamide, alone or in combination, have lead to a reported 50% reduction in tumor size but with limited durability (20). The use of chemotherapy in the adjuvant setting with surgery or with surgery and radiation has shown mixed results with some studies indicating increased survival while other failing to show improved survival. Dr. Hendrick found expression of PDGF on fibroblasts in vaccine-associated sarcomas while non-vaccine associated tumors did not express PDGF, suggesting the biological basis for the use of tyrosine kinase inhibitors in the management of these tumors (9). The use of tyrosine kinase inhibitors to block PDGF receptor signaling has been observed to have some activity against this tumor in a limited number of cases (11). The best results have been reported with combinations of aggressive surgery, radiation, and chemotherapy with radiation providing the most consistent benefit when added to surgery. Prognosis is roughly (based on an average of reported studies) marginal resection disease free interval of 79 days versus wide surgical excision 325 days. These also correspond to survival of greater than 16 mos with wide excision versus 9 mos with marginal resection (45). Surgery plus radiation leads to survival of about 650 days while surgery plus radiation and chemotherapy is around 700 days (28,29,30).

VI.Prevention

Given the high cost of treatment and relatively poor prognosis with vaccine associated sarcoma, prevention is highly desirable. The clear association between vaccination and tumor development in cats is well accepted, thus recommended vaccine protocols with less frequent vaccinations are desired. The use of vaccines and other injectables that produce less or no inflammation at the injection site are recommended. Although chronic inflammation alone is not thought to cause malignant transformation it is a well-accepted tumor promoter, and combined with other vaccine components and host factors likely plays a significant role in the pathogenesis of injection site sarcomas. Chronic inflammation that has a high fibrous proliferative component has been found to be of the highest risk in other species. Indeed, not all substances that produce inflammation under the skin provide equal risk, which may be related to the oxidative character of the substance that may induce tumor initiation. The qualitative rather than the quantitative nature of the inflammatory response to the substance or foreign body, and host factors such as genetics, are also like to play a significant role in tumor development. The veterinarian can't control the cat's genetics, but can choose not to introduce substances, be they antibiotics or vaccines, that induce chronic inflammation and fibrous proliferation under the skin in cats.

Summary

Our understanding of feline vaccine-associated sarcomas and their management and treatment remains incomplete. Yes, we have broadened our knowledge and understanding of the mechanisms that contribute to the development of this disease significantly over the last few years through extensive research, but there still remains much to learn. Controversy about the existence of vaccine-associated sarcomas is much less now than 20 years ago. Given that these tumors have been described, albeit far less frequently, following the administration of modified live vaccines and other injectables prior to the introduction of adjuvanted vaccines in 1985, it's hard to ignore the 61% increase in fibrosarcomas at injection sites within a few years after their introduction.(1,27,6,23,24,47) Though this iatrogenic cancer may never be completely eliminated, I am confident that its prevalence can be significantly reduced, and those cats that are afflicted with the disease will be diagnosed in earlier stages and more effectively managed by the informed veterinarians.

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