Induced or Injection Site Sarcomas:

WHAT DO WE REALLY KNOW?

Merck Animal Health provides this editorial to you as part of our commitment to ongoing practitioner education. The views and opinions expressed by Dr. McGill in this editorial are solely his own. We encourage you to learn more about the important topic of possible vaccine-related feline sarcomas.

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Induced or injection site sarcomas are soft tissue sarcomas that have been associated with vaccinations and other injections. There continues to be controversy over the etiology of these tumors. They are so rare that confirming association with any specific material cannot be confirmed with scientific certainty. Some colleagues have the opinion that these tumors are related to specific vaccination programs and processes. These opinions have been expressed as fact without scientific evidence, causing much confusion in veterinary medicine. Some of these thoughts, ideas, and discussions have been presented out of context and has resulted in unfortunate distribution of unsubstantiated information.

No links between induced or injection site sarcomas and specific materials can be confirmed.

BACKGROUND

This tumor association with injections was suggested in 1993 by pathologists observing these reactions in cats. There was much discussion occurring at that time, with many associating this process with adjuvanted vaccines and in particular aluminum. The Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) was formed. This task force was supported by veterinary medical associations and most of the vaccine-producing companies. Their final conclusions were controversial and inconclusive.[1] These findings are not unexpected due to the rarity of this tumor process. Many epidemiologic and commentary

articles were published to assist veterinary medicine in understanding induced or injection site sarcoma. Cause and effect has not been confirmed with any of these studies.

Though many studies have been published on this sarcoma, cause and effect has not been confirmed with any of them.

LINKS TO INJECTABLE PRODUCTS

Since those studies were published, epidemiologic studies have associated various injectable products with the induction of these tumors. This includes non-adjuvanted products such as modified live products and recombinant products (Table 1).

Some colleagues have opined that aluminum adjuvant was the major cause of this tumor. In our pathology practice, aluminum is rarely identified with these

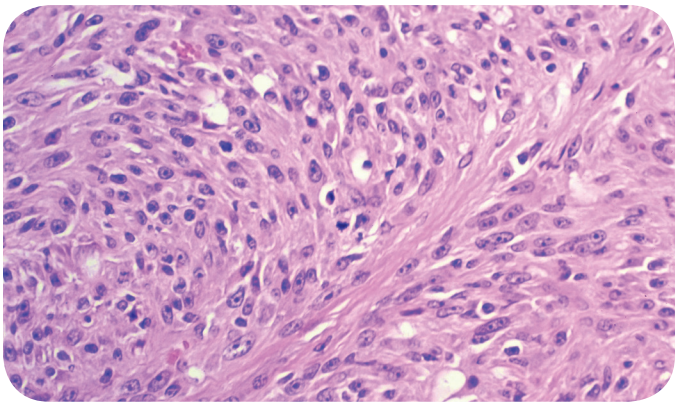
Table 1.

Feline injection site fibrosarcomas reported to the Veterinary Medicine Directorate (UK) by type of injectable product

	Live vaccines	Inactivated vaccines	Recombinant vaccines	Mixed vaccines	Other products
2006	23	6	NR	9	1
2007	38	10	NR	7	4
2008	21	8	5	2	6
2009	16	10	4	5	5
2010	30	11	9	2	1
2011	20	3	2	7	2

NR=Not reported.
Other products: Unidentified vaccine (3), antimicrobial (4), anti-inflammatory (4), insect growth regulator (3), ectoparasiticide (2), insulin (1), anthelmintic (1), cardiovascular product (1).
Source: Veterinary Medicine Directorate (VMD).

Figure 1. Sarcoma cells with pleomorphic patterns and scattered mitotic figures.



tumors in recent years. This writer has suggested from the initiation of discussion of these sarcomas that aluminum was only a part of the process. Continued observations have supported that conclusion.

What we think we know about these tumors is that they primarily occur in cats. Veterinary pathologists have recognized these tumors in dogs, horses, ferrets, and some zoo animals. Induced sarcomas are known to occur in humans.

DETERMINING TRUE INCIDENCE UNDERMINED BY DEFICIENCIES IN REPORTING

The incidence of these tumors is speculative. Part of the reason is due to the fact that the tumor is not a reportable disease. If you see one, it should be reported to the vaccine manufacturing company. The most common incidence number being discussed by most authors is 0.5–2 per 10,000 vaccinations administered. This is a wide range, but the incidence is likely within or close to this range. There appears to be little evidence that this incidence is decreasing. It is so rare that some veterinarians may never see this tumor and others may see no more than one. The concern is that when it does occur in a cat, the incidence is essentially 100% in that pet, which can result in a communications challenge with the owner. This communication challenge is complicated by massive amounts of information available on the Internet—much of which is unsubstantiated.

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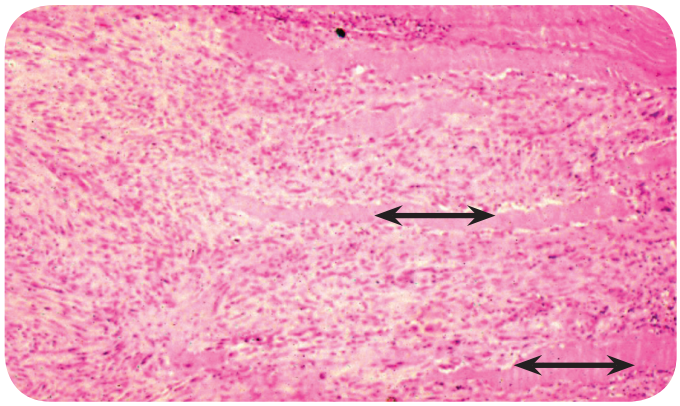
Figure 2. An injection site sarcoma invading muscle.



PATHOLOGY OF INDUCED OR INJECTION SITE SARCOMAS

Veterinary pathologists have observed a characteristic histologic pattern with these sarcomas. The cells are highly anaplastic and most commonly have a high mitotic index (Figure 1). There is a necrotic center that may be due to rapid growth of these tumor cells. A mixed cell inflammatory response surrounds the tumor diffusely or focally with a preponderance of lymphocytes and macrophages. The macrophages contain vacuolated cytoplasm with rare cases containing blue-gray material (aluminum). The presence of aluminum when this tumor was first observed suggests that vaccine granulomas may be involved. Vaccine site granulomas are much more common than sarcomas.

Induced sarcomas are extremely invasive (Figure 2), particularly in loose tissue such as the connective tissue between the shoulders. Some of these tumors have demonstrated projections of tumor cells as much as 13–15 cm from the site of induction. This is mainly between the shoulder blades. This means that extensive excision is required for surgical excision. Survival of affected cats is associated with completeness of the first surgical excision.

This observation has resulted in the VAFSTF recommendations for handling these tumor masses at an injection site[2]:

- Biopsy (remove): if present 3 months after injection
- Biopsy (remove): if >2 cm in diameter
- Biopsy (remove): if the injection site is increasing in size 1 month after injection

RECENT DEVELOPMENTS

A recent study published in the *Journal of American Veterinary Medical Association* has added epidemiologic information to veterinary medicine, but may also add confusion for some colleagues.[3] This was a small study that was initiated as a much larger study; however, many of the expected data sources were not available. The size of the study and the availability of limited follow-up decreased the effectiveness of the study. There is still some good information to glean. The study supported the United Kingdom data that all immunization products are likely associated with this induced tumor and recombinant vaccines are not free of risk.[2] In light of this study, anecdotal observations and the United Kingdom data, "no vaccine can be assumed to be risk-free in a susceptible individual." Other products that are injected are associated with induction of the sarcoma. The higher association with vaccines is likely due to the propensity of their use. The most important statement in the article is in the last paragraph:

> "However, the findings of this study should be reassuring in that the use of medically indicated products does not appear to be associated with substantial morbidity of sarcomas, and their propensity to cause tumors appears to be small."[3]

All immunization products are likely associated with this induced tumor, and recombinant vaccines are not free of risk.[2]

THE ROLE OF GENETICS

More and more colleagues are of the opinion, of which I agree, that the major problem with this tumor process is the cat and the likely genetic predisposition. If the genetics of the cat could be altered, this tumor would be even rarer. The problem is that this will never happen. Now that we know about this tumor, it will be observed from now into the distant future. This type of tumor has been observed before in the cat. Induced tumors occur in the cat with trauma to the eye, resulting in lens rupture with induction of a sarcoma that often is an osteosarcoma within the globe of the affected eye.

Researchers are investigating the genetic changes that occur in these tumors in the cat. Their goal is to identify a specific or several genetic abnormalities within these tumor cells. This would assist in confirming whether the specific tumor excised is an induced sarcoma. This may be helpful if they are successful. My concern is that these tumors are so aggressive that a single or group of genetic abnormalities may not include all of the genetic defects that are likely to be associated with these sarcoma cells. In other words, there may be multiple clones of cells in each tumor that may result in this aggressive sarcomatous pattern.

CONCLUSIONS

- Injection site sarcomas are rare
- Remember the 3-2-1 recommendations for biopsy
- Immunization is a medical procedure (err toward overimmunization)
- Document, document, document
- At this time, it is not known for certain that non-adjuvanted products will produce fewer tumors (non-adjuvanted products are associated with tumors)
- The only means of completely eliminating these tumors is modifying the cat genome
- The choice of vaccines becomes a weighing of cost, efficacy, compliance, and practicality

References: 1. Vaccine-Associated Feline Sarcoma Task Force. The current understanding and management of vaccine-associated sarcomas in cats. *J Am Vet Med Assoc.* 2005;226(11):1821–42. **2.** American Veterinary Medical Society. Vaccine-Associated Feline Sarcoma Task Force guidelines—diagnosis and management of suspected sarcomas. Available at: https://www.avma.org/About/AlliedOrganizations/Pages/tfguidelines99.aspx. Accessed June 12, 2013. **3.** Srivastav A, Kass PH, McGill LD, Farver TB, Kent MS. Comparative vaccine-specific and other injectable-specific risks of injection-site sarcomas in cats. *J Am Vet Med Assoc.* 2012;241(5):595–602.

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