Feline postvaccinal sarcoma: 20 years later *

Abstract

The first reports of feline high-grade fibrosarcomas occurring at sites traditionally used for vaccination appeared in 1991 and were based on a series of cases seen by veterinary pathologists over the preceding 5 y in the northeastern United States (1). Soon such tumors were being reported from all over North America and Europe, stimulating a great deal of debate, speculation, recrimination, and investigation over the ensuing 10 years (2–4). Our understanding of the disease was initially hampered by poor vaccination records, poor long-term clinical follow-up information, and refusal by vaccine manufacturers to disclose proprietary information about vaccine formulation. Information gathered from histologic assessment of these sarcomas, retrospective and prospective clinical studies of tumor behavior, and epidemiologic studies assessing prevalence and causation have gradually brought us to a consensus about most aspects of this disease (5). Along the way to that consensus, this disease triggered some recommendations for profound changes in how we vaccinate cats, what we use to vaccinate cats, and indeed how we think about vaccination in general (6,7). While there are still some issues being debated as to what products have been proven to cause sarcomas at the site of previous administration and exactly how those sarcomas evolve, the following clinically relevant points have broad general agreement:

1. The only *proven* cause for injection site sarcomas in cats is prior administration of a killed, adjuvanted vaccine. Rabies and leukemia vaccines are the only ones with solid causal associations (4,8). Claims implicating other agents such as lufenuron or microchips are unsubstantiated because previous vaccination in that same location could not be ruled out. The abrupt and dramatic increase in the prevalence of these sarcomas may have been related to a change in legislation in the United States in 1985, requiring the use of killed vaccine rather than modified live rabies vaccine in cats (5).
2. The interval between vaccine administration and detection of sarcoma can be as short as 4 mo and as long as 13 to 15 y. Most probably occur within 1 to 3 y. This long potential lag time, not initially recognized, has resulted in great confusion about which products can cause sarcomas, and which product caused the sarcoma in any individual patient (5).
3. The tumor arises via malignant transformation of reactive fibroblasts at the periphery of a nodule of necrotizing and granulomatous cellulitis at the site of previous vaccination. Only a small proportion of such nodules, estimated at 5% in one study (9), is destined for malignant transformation, and the risk does not justify routine excision of these nodules. The magnitude and duration of that inflammation is probably influenced by variables in vaccine formulation and genetically conditioned patient response. The resulting tumor is a high-grade sarcoma with considerable phenotypic variation resulting in histologic diagnoses of fibrosarcoma, osteosarcoma, chondrosarcoma, or other high-grade stro-mal sarcomas. At least 80% are histologically classified as fibrosarcoma. There is no prognostic significance to these distinctions.
4. Most estimates of prevalence are between 1 in 1000 and 1 in 10 000 vaccinations (3,4,10,11). Although that risk seems very small, this still means that we probably initiate 300 to 500 postvaccinal sarcomas every year in Canada and an estimated 2000 per year in the United States (12). These estimates are based on cases submitted for histologic confirmation. The true prevalence is likely to be higher.
5. The diagnosis of postvaccinal sarcoma requires that the lesion possess a specific set of histologic features, and that it occurs at an anatomic location proven or reasonably assumed to be a site of previous vaccination. The histology by itself may be strongly suggestive, but it is not absolutely specific in distinguishing vaccine-associated from spontaneous (non-vaccine-associated) fibrosarcomas. Typical features include profound anisokaryosis and hyperchromasia, cellular gigantism, numerous mitotic figures, liquefactive necrosis, and numerous lymphoid aggregates around the periphery of the tumor (5,13,14).
6. These tumors are deceptively invasive and have an extremely high risk of postoperative recurrence even when both the surgeon and the pathologist agree that the initial excision appeared to be curative (15,16). The metastatic risk was originally assumed to be very low, but in fact the risk probably increases with the survival time of the cat. It is uncertain whether this increased metastatic risk is just because cats receiving

aggressive treatment survive longer and therefore are more likely to express metastatic disease, or whether some treatments may themselves directly promote metastasis. In those cats receiving very aggressive treatment (radical excision, radiation, and chemotherapy) and therefore surviving what previously was rapidly fatal disease, the prevalence of metastatic spread may reach 22% (5). Reports of disease-free intervals, survival times, and case fatality rates are almost uninterpretable because of vast differences in surgical and medical treatment protocols and in the definition of what constitutes a tumor-associated death (5,12,15,16). The one clear trend, however, is for increased disease-free intervals with more aggressive initial surgical excision that achieves wide margins.

Information about various clinically relevant aspects of this disease and the recommendations for changes in vaccination protocol were widely publicized in the 2 y following the formation of the Vaccine-Associated Feline Sarcoma Task Force in 1996. In the *Journal of the American Veterinary Medical Association* alone, 16 papers were published within 2 y of the formation of the task force, and a special Feline Postvaccinal Sarcoma Symposium was held at the 1998 annual meeting of the American Veterinary Medical Association. The interest in the disease and rate at which new information was being published began to decline by about 2004, and the Vaccine-Associated Feline Sarcoma Task Force was disbanded in 2005.

There was a general assumption that the changes in recommended feline vaccination protocols (calling for more selective use of leukemia vaccination and less frequent vaccination for rabies, as well as vaccination sites more amenable to amputation) should decrease the prevalence of this disease and, especially, increase the surgical cure rate. It was also hoped that the introduction of virus-vectored, non-adjuvanted rabies (and, later, leukemia) vaccines that cause little or no inflammation at the site of vaccination would further contribute to a gradual decline in disease prevalence. If these optimistic assumptions were correct, we should by now be seeing a decrease in overall disease prevalence, or at least a shift in the mean age of affected cats to an older age group that is still being affected by the vaccine products and practices in place when they were young (prior to 1996). Is there any such evidence?

A recent study by Shaw et al (17) to assess the impact of changing vaccine practices on various characteristics of postvac-cinal sarcomas was based on case records from 392 confirmed postvaccinal sarcomas in the United States from the years 1990 to 2006. This study concluded that there had been a significant shift in the location of these sarcomas that corresponded to the sites recommended by the Vaccine-Associated Feline Sarcoma Task Force in 1996 (6) and adopted by the American Association of Feline Practitioners in 1997. Prior to 1996, the majority of postvaccinal sarcomas were found in the inter-scapular region, with tumors in this location occurring 5 times more frequently than in any other location. After 1996, there was a statistically significant shift in tumor location from the interscapular region to the hind legs and immediately adjacent areas. There was no apparent shift in the age of affected cats, and the study design did not allow any investigation of changes in overall disease prevalence (17).

We have been tracking the prevalence of postvaccinal sarcomas in biopsy submissions from across Canada for the past 19 y, and present that information here. In Tables 1 and and22 and Figure 1, we present the overall prevalence of this diagnosis as a proportion of all feline skin and subcutaneous mass submissions over the 19-year interval from 1992 to 2010 inclusive. We also looked specifically at whether or not there was any change in disease prevalence or the mean age of affected cats as a result of 2 potentially significant historical events. The first was the 1996 publication of the recommendations for changes in vaccination protocols and the subsequent flurry of conference presentations and clinical publications. The second was the introduction in Canada of the first non-adjuvanted canarypox-vectored rabies vaccine for cats (Purevax; Mérial, Duluth, Georgia, USA) in the year 2000.

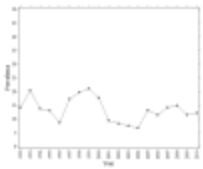

Figure 1
Prevalence of feline postvaccinal sarcomas as a percentage of skin masses examined.

Table 1

Prevalence of postvaccinal sarcomas among feline skin masses (1992–2010)[a]

Year	Number of feline submissions	Number of feline skin masses	Number of postvaccinal sarcomas	Number of postvaccinal panniculitis	Postvaccine sarcomas/sl masses (%)
1992	1127	162	23	0	1
1993	867	108	22	0	2
1994	1092	145	20	0	1
1995	1498	198	26	0	1
1996	1741	253	22	3	1
1997	2222	359	62	10	1
1998	2746	519	102	38	1
1999	3006	559	118	54	2
2000	3333	637	113	76	1
2001	3587	1079	103	48	1

Table 2

Mean age of cats with postvaccinal sarcomas (1992–2010)[a]

Year	Number of feline postvaccinal sarcomas	Mean age (standard deviation) in years	95% confidence interval
1992	23	9.3 (3.9)	7.6–11.0
1993	22	9.6 (4.0)	7.9–11.4
1994	20	9.6 (3.2)	8.1–11.1
1995	26	8.6 (3.9)	7.1–10.2
1996	22	9.8 (3.3)	8.3–11.3
1997	62	9.6 (3.7)	8.6–10.5
1998	102	9.4 (3.7)	8.7–10.1
1999	118	9.8 (3.5)	9.2–10.4
2000	113	9.0 (3.5)	8.3–9.6
2001	103	9.4 (3.5)	8.7–10.1
2002	97	10.6 (3.1)	10.0–11.2

The diagnoses reported here were all made by one pathologist based on histologic assessment of incisional or excisional biopsies from about 800 veterinary clinics across Canada. Tentative diagnoses based on cytology samples were not included because such diagnoses are not sufficiently reliable. The criteria for making the diagnoses were an anatomic location compatible with traditional vaccine sites (interscapular, paravertebral soft tissue, proximal rear legs), and identification of a high-grade stromal tumor with histologic features compatible with those previously described for postvaccinal sarcomas (5,13,14,18). Cases with typical histology but an atypical anatomic location (or with no recorded anatomic location) were excluded.

Our results indicate that there has been no meaningful change in overall disease prevalence over the past 19 y (Table 1, Figure 1). There has been no apparent decrease in overall prevalence in response to intense publicity about the disease and recommended changes in vaccination protocols initiated in 1996, or in response to the introduction of the non-adjuvanted rabies vaccine (Purevax; Mérial) in the year 2000. In fact, there was even a small increase in the absolute number of postvaccinal sarcomas and the relative proportion of postvaccinal sarcomas among all feline skin and subcutaneous masses during the 4 y (1997 through 2000, inclusive) following the widespread promotion of the changes in vaccination practices (Figure 1, Table 1). Since there was also a sharp increase in the number of submissions of postvaccinal panniculitis during that same interval, we interpret this change to reflect increased awareness by owners and veterinarians of the existence of this disease and the importance of early surgical removal and histologic assessment. The proportion of skin masses diagnosed as postvaccinal sarcomas actually decreased slightly in the years 2001–2004 because of the overall increase in the submission of feline skin masses in general and postvaccinal panniculitis in particular, representing “false alarms” as a reflection of increased practitioner vigilance. These trends all simultaneously disappeared in 2005, in parallel with an obvious decrease in the number of journal publications and conference proceedings related to feline postvaccinal sarcomas. That was the same year in which the Vaccine-Associated Feline Sarcoma Task Force was disbanded. This may have led to the assumption that the disease itself had also virtually disappeared, but our data contradict that assumption. We compared the proportion of postvaccinal sarcomas in the first 5 y of our study (1992–1996) to the proportion in the last 2 y (2009–2010). That proportion remained identical at 13% of all feline skin mass submissions. We acknowledge that our prevalence data reflect biopsy submissions and probably underestimate the true disease prevalence. On the other hand, histologic assessment is the only reliable way to establish the diagnosis, and it has also been the basis for all previous estimates of disease prevalence.

Our hope that the disease prevalence would gradually decrease as the older cats died and that younger cats entering the sample pool would have benefited from the changes in vaccination protocol and formulation has received no support from our data as presented in Table 2. The highest prevalence has remained in the 9- to 14-year-old age group as previously reported (17). To evaluate the potential impact of these pivotal events on the age of affected cats, we compared the mean age of the 90 affected cats during the 4 years 1993–1996 with the mean age of the 168 affected cats in the 2 years 2009–2010, using a 2-sample *t*-test. The mean age of affected cats during the 2009–2010 interval was significantly higher (10.5 ± 3.6 y) than the mean age of affected cats during the 1993–1996 interval (9.4 ± 3.6 y) ($P = 0.0157$). The small statistical difference lost clinical credibility, however, when we evaluated the age of the cat population in general for those same intervals. The mean age of all cats in our biopsy population is also significantly higher in the 2009–2010 interval than in the 1993–1996 interval (9.4 ± 4.7 y versus 8.2 ± 5.0 y) ($P < 0.0001$). Cats with postvaccinal sarcoma have indeed become a little older (a mean increase of 1.1 y) at the time of initial diagnosis, but the mean age of cats in general within the biopsy population increased by the almost identical figure of 1.2 y.

When we tried to explain the failure of postvaccinal sarcomas to diminish in prevalence, we initially assumed that this might be because the 1996–1997 recommendations by the Vaccine-Associated Feline Sarcoma Task Force and the American Association of Feline Practitioners regarding changes in vaccination practices had not received widespread support. Our data indicate that this is not true: the abrupt increase in the number of "potential" sarcoma submissions indicate that practitioners in Canada had obviously become very aware of the existence of postvaccinal panniculitis and its potential sequel of postvaccinal sarcoma. In the United States, Shaw et al (17) reported a rapid shift in anatomic origins for postvaccinal sarcomas in California from interscapular to hind limb following those 1996 recommendations, implying a very high level of acceptance of the recommended changes in sites of vaccination. One additional study of North American feline vaccination practices from 1998 to 2002 also indicated very high compliance among practitioners (9). Although we have concerns about the validity of this study because the data are based on input from only 40 veterinary practices out of an initial pool of 166 practices from the United States and Canada that fully participated in a voluntary web-based survey, it is still the only study to provide any direct information about practitioner compliance with the recommended changes. In that study, almost 80% of approximately 30 000 doses of rabies and leukemia vaccines were given in the recommended sites. We have no direct evidence about whether or not other recommendations, particularly recommendations to reduce the frequency of vaccination for both rabies and leukemia, have received similar support.

We had also expected that the introduction of a canarypox-vectored non-adjuvanted rabies vaccine (Purevax; Mérial) in Canada in 2000 would cause a noticeable decrease in disease prevalence. Non-adjuvanted, virus-vectored vaccines do not cause significant and persisting inflammation at the site of administration (5,19) and therefore should not cause sarcomas. The failure to detect any meaningful change in the prevalence of postvaccinal sarcomas or in the age of affected cats subsequent to the introduction of that vaccine could mean that there has not been a significant shift from traditional adjuvanted vaccines to this new product, but in fact we have no actual information about how widely this product is being used across Canada. Its popularity may be limited by its higher cost when contrasted to traditional adjuvanted vaccines, but the major barrier to its widespread use probably stems from the fact that it is approved for use only as an annual vaccine. The availability of adjuvanted vaccines approved for use every 3 or even 4 years creates a substantial marketing advantage for those products. Since the risk of postvaccinal sarcoma has been estimated at between 1 in 1000 and 1 in 10 000 vaccinations, the risk may not be high enough to dissuade practitioners from using the more economical adjuvanted products that also fit better with the general recommendation that we should be vaccinating only as often as necessary. We view this as an ethical dilemma: do we continue to use products that are less expensive and require administration only every 3 to 4 y, and simply accept the risk of producing 1 or 2 postvaccinal sarcomas every year in a typical busy small animal practice? Or do we adopt the "do no harm" approach and routinely use (or at least offer) the non-adjuvanted vectored vaccine because of its greater safety? Should we, as a matter of policy, explain and offer both options to cat owners? These are questions worth debating. CVJ

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