Current thinking on feline injection site sarcomas

Dr Andrew Sparkes BVetMed PhD DipECVIM MRCVS
Veterinary Director, International Cat Care & International Society of Feline Medicine

September 2013

Feline injection site sarcomas (FISS) are a rare occurrence, but when they do occur they can have devastating consequences for the individual cat. Understandably the condition causes considerable concern among both veterinarians and owners, but to address this issue properly requires careful consideration of the known facts. This article attempts to briefly review both historical and contemporary data on FISS to enable rational conclusions to be drawn over how to try to manage the issue.

Historical aspects
An awareness that injectable may sometimes have the ability to trigger sarcoma formation in cats first came to light in the early 1990s when publications appeared in the American literature potentially linking the development of fibrosarcomas to injection sites. At around the same time, there were also reports of very severe local reactions (necrotizing panniculitis) in some dogs and cats inoculation with rabies vaccines. Early reports, of what was initially termed vaccine-associated sarcomas (VAS), suggested that these occurred more commonly with the use of adjuvanted vaccines and especially with the use of rabies and FeLV vaccines. An observed apparent rise in the prevalence of this type of fibrosarcoma also appeared to occur co-incidentally with changes in legislation that mandated rabies vaccination, adding further speculation to the role of rabies vaccines in tumorigenesis. Early (though somewhat limited) epidemiological studies appeared to confirm the link between rabies and FeLV vaccination and an increased risk of sarcoma formation, and also identified an increase risk with the injection of multiple vaccines at the same site. By the mid to late 1990s, several studies and publications on VAS had appeared. A number of these had attempted to quantify the risk of sarcoma formation, and estimates varied between around 2 and 36 cases of sarcomas for each 10,000 doses of vaccine administered. Some, but not all, reports still suggested a link between rabies and/or FeLV vaccination, but it became apparent that other vaccine antigens (eg, herpesvirus, calicivirus and parvovirus - FVRCP) may also be linked to VAS.
A common assumption was that sarcoma formation was linked with inflammation induced by the vaccine at the site of injections. This was based partly on the knowledge that VAS were commonly associated with a marked inflammatory response, and partly with the knowledge that some vaccines produced greater inflammation than others at the site of inoculation. Nevertheless, a direct link between administration of vaccines that caused greater local inflammatory reactions and an increased risk of subsequent sarcoma formation was never demonstrated.

**More recent studies**

In 2002 and 2003 two larger epidemiological studies from North America were published – one study followed more than 30,000 vaccinated cats for a period of 1-3 years, and the second was a multicentre case-control study looking at nearly 1500 cats. These were much more substantial studies than had been published previously and suggested that the risk of vaccine-associated sarcomas may be much lower than previous estimates (in the order of 1 per 30,000 doses of vaccine) and further, that VAS were not associated with any particular manufacturer or brand. In fact no increased risk was found even with the use of killed, adjuvanted or multidose vaccines in the case-control study. However, the possibility of injectable products other than vaccines also being associated with the formation of some sarcomas was noted. The 2003 case control study reported by Kass and others in JAVMA concluded that the results did not
support the superiority of any single vaccine brand for preventing vaccine-associated sarcomas, and that their results were consistent with the concept that the vaccine alone was insufficient to cause a sarcoma (but may be a contributory factor in some cases, along with other factors such as underlying genetics).

A further study published in 2007 evaluated adverse vaccine reactions recorded in cats vaccinated at Banfield Pet Hospitals in North America. The study looked at adverse reactions that occurred within 30 days of vaccination and then followed the cats for a further 1-2 years. They reported an adverse reaction rate in cats of around 0.5% (2,560 cases out of over 469,000 vaccines administered) with the most common being lethargy (± fever) in 54%, local reactions in 25%, vomiting in 10%, facial oedema in 6% and pruritus in 2%. None of the cats that developed localised reactions developed a sarcoma at the injection site in the 1-2 years during which they were monitored, and no VAS were identified among the nearly 470,000 cats vaccinated, again in contrast to earlier much higher estimates of prevalence. (ref)

Along with these data, case reports have emerged linking the occasional development of subcutaneous sarcomas in cats with the use of other ‘injectable’ products, including glucocorticoids, NSAIDs, cisplatin, lufenuron, non-absorbable suture material and microchips. With these data and the knowledge from epidemiological studies, this syndrome was renamed feline injection-site sarcomas (FISS) rather than VAS to more accurately reflect our current state of knowledge, and the apparent risk with a variety of injectable products.
While studies looking at the severity of post-vaccination inflammation at the injection site failed to show a clear direct link with the risk of sarcoma formation, other investigators looked at potential genetic traits that may increase the risk. Although no breed-associated risk has been identified, one study from the USA did suggest that polymorphism in the p53 tumour suppressor gene was significantly associated with an increased risk of FISS. However, another more recent study from Germany was unable to substantiate this finding, and further work is clearly needed in this area.

Most information about FISS has come from studies and publications in the USA. However, FISS are seen worldwide and a recent study looked at cases seen in the UK in 2007. This study estimated the frequency of FISS to be around 1 per 17,000-50,000 cats registered at practices, or 1 per 5,000-12,500 vaccine visits. The authors concluded that the frequency of FISS was very low (and similar to estimates from the USA), that evidence of a causal relationship between FISS and vaccination remains weak, and that many other diseases have a much greater impact on feline health and remain more important targets for improving feline welfare.

Srivastav and others published a further case-control study of FISS in the USA in JAVMA in 2012. In that study, comparing controls cats with those that developed sarcomas in the inter-scapular region there was no significant difference in the use of inactivated and recombinant rabies vaccines, between the use of inactivated and recombinant FeLV vaccines and between the use of inactivated and live FVRCP vaccines. Comparing the same data for cats that developed sarcomas in the hind-
limb regions, there was also no significant difference in the use of inactivated and live FVRCP vaccines, but evidence of a significantly higher use of inactivated rather than recombinant rabies vaccines in the sarcoma group. However, the study authors noted that all vaccine types appeared to be associated with some risk of FISS, and there appeared to be a trend for a higher risk with the use of modified live FVRCP compared with inactivated FVRCP. This study also highlighted that of all the cats that developed sarcomas at potential injection sites, only 56% were reported to have received vaccinations and 13% had received another injectable product. An increased risk of FISS was again noted with the injection of a variety of glucocorticoid products.

Where do these studies leave us now?

Feline injection site sarcomas remain an enigmatic problem. While unequivocally serious and even devastating when they arise, they are fortunately rare. Current and most reliable estimates suggest they may occur with a frequency of around 1 for every 10,000-30,000 vaccines, and it is clear that vaccines are not the only injections associated with their development. The relatively rare nature of these tumours means that studying causal and contributory factors to their development is very difficult. The current belief is that vaccines and a number of other (potentially all) injectable products may have the ability to contribute to sarcoma formation (as may other forms of tissue trauma). It is thought likely that inflammation at the injection site and the genetic make up of the cat may
contribute to the risk of sarcoma development, but these are all putative risks rather than being proven, and the exact relationship between any of these and the development of sarcomas remains elusive.

It seems clear that in contrast to the early reports of FISS, these are not linked primarily with FeLV or rabies vaccination, but in fact all vaccines appear to carry a risk. Whether this is because early studies were based on a limited number of cases, or whether it is because of changes in vaccine formulation since the initial reports remains unknown. However, it seems clear that all vaccines carry some risk of being a contributory factor in triggering sarcoma formation in some cats.

As clinicians, the question remains as to how we can best approach minimising the small risk of FISS occurring in our patients. Until our understanding of the aetiopathogenesis of these tumours improves this remains challenging. However from current evidence and the accumulated data reviewed here it is possible to develop a rational and pragmatic approach:

It should be recognised and communicated with clients that this is a rare problem, although serious when it occurs. Sarcomas are seen as a spontaneous disease, but there is evidence that many (if not all) injectable products may have a role in increasing the risk in some cats. It is likely that vaccines carry a higher risk than other injectables, but the association with vaccines is not unique.

Searching for a ‘perfect’ vaccine that is safe, efficacious and has no ability to be involved in triggering a sarcoma formation is likely to be futile. All vaccines appear to carry a risk, and this is not (as previously
thought) particularly associated with rabies or FeLV vaccines or even with adjuvanted vaccines.
At present we have no way of identifying which population of cats might be more at risk of developing FISS, or of other factors involved that may enable preventative measures to be taken.
Reducing the frequency of vaccination and avoiding unnecessary vaccination while maintaining the protective benefits of vaccination is a sensible and logical approach to helping reduce the prevalence of vaccine-associated adverse events. Both the AAFP and WSAVA (and other veterinary organisations) have recommended a reduced frequency of vaccination in many situations for at least some vaccine components. As the risk of FISS cannot be prevented (other than by avoiding injecting cats entirely, which would cause vastly more health and welfare problems), and as the risk is actually very low, a more important priority is to monitor cats carefully after vaccination. Although not subjected to critical scientific appraisal, the so-called ‘3-2-1 rule’ would seem highly appropriate to emphasise – any local swelling at the site of vaccination that persists for 3 months after vaccination, and/or is greater than 2cm in diameter, and/or is getting larger 1 month after vaccination should be biopsied and dealt with according to the histopathological diagnosis. It would also seem prudent to apply this rule to the use of all injectable products and not just to single out vaccines. Client communication and vigilance are vital in this.
Following the AAFP recommendations on the site of vaccination – subcutaneously in the left hind-leg for FeLV, the right hind-leg for rabies
and the right foreleg for other vaccines, and trying to use a site distal in the limbs is also a very sensible approach. It may allow for easier monitoring of the injection site by owners, and will certainly facilitate surgical removal of an aggressive tumour with appropriate margins should one arise. Again, given our current knowledge, it might also be argued that other injectable products may also benefit from being administered subcutaneously in the distal limb where possible and appropriate.

Keeping a perspective on the true prevalence and risks of FISS occurring should help in formulating rational and informed approaches to managing the problem. While the unnecessary use of injectable products should be avoided, the very low risk of FISS formation should not preclude their use, especially when the health benefits of something like vaccination clearly vastly outweigh the very small risk of FISS development. Further work is clearly needed though to understand how injectable products may contribute to sarcoma development, what cats might be at increased risk of this occurring and how, if possible, this might ultimately be prevented. In the meantime, vigilance after using injectable products is perhaps the best way of minimising the impact of sarcoma formation, should it arise.

References and further reading:


Mucha D, Laberke S, Meyer S, Hirschberger J. Lack of association between p53 SNP and FISS in a cat population from Germany. Vet Comp Oncol. 2012;9999


