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Review article
Ανασκόπηση

Injection site sarcomas in other species than the domestic cat

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ABSTRACT: Injection site sarcomas (ISS) are tumours of tissues of mesenchymal origin that occur at an injection site. These tumours have been mainly described in cats as Feline injection-site sarcoma (FISS), but suspected cases have also been described in other species such as dogs. In other species than the domestic cat, these tumours are however much rarer. As a result, the body of literature is limited. This review aims to summarize the knowledge regarding ISS in species other than the domestic cat. In general, it seems that ISS can occur in a wide range of animals and that similar treatment strategies are employed as in cats. Like in cats, it seems that the benefit of the reasons for injection (such as vaccination and microchip implantation) could outweigh the risk of ISS development in other species.

Keywords: Injection site, sarcoma, oncology, cancer, animals

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INTRODUCTION

Injection site sarcomas (ISS) are tumours of tissues of mesenchymal origin that occur at an injection site (Zabielska-Koczywąs, Wojtalewicz, et al., 2017). These tumours have been mainly described in cats as Feline injection-site sarcomas (FISS), where they occur in about 1-10 of every 10,000 vaccinations (Zabielska-Koczywąs, Wojtalewicz, et al., 2017). A chronic inflammatory response at the injection site has been described as the hypothesis for the neoplastic disease (Woodward, 2011; Hartmann, Day, et al., 2015). Several studies have been conducted to investigate FISS. This includes studies regarding, among others, treatment strategies (Cohen, Wright, et al., 2001), risk factors (Kass, Spangler, et al., 2003) and immunohistochemistry (Carneiro, de Queiroz, et al., 2018). The current state of knowledge was summarized in several reviews (Saba, 2017; Zabielska-Koczywąs, Wojtalewicz, et al., 2017).

In addition to cats, suspected cases of these tumours have also been described in other feline species such as a lion (Kinne and Tarello, 2007) and in non-feline species such as dogs (Jacobs, Poehlmann, et al., 2017).This type of cancer is however very rare in other species than the domestic cat. As a result, the available literature about the condition in these species is sparse.

Due to the role of dogs as companion animals and the frequency of injections (e.g. for vaccinations and microchip implantations) performed, it is useful to also investigate ISS in these animals. Furthermore, investigating ISS in more exotic animals could provide more information on the condition in general and assess what factors (e.g. risk factors and treatment outcomes) are species-specific and which factors can be generalized.

The current review aims to briefly summarise the limited evidence about this condition in other species than the domestic cat.

SEARCH STRATEGY

To identify relevant literature regarding injection site sarcoma the Pubmed, Pubmed Central, Google Scholar and Web of Science databases were searched. Database-specific variants of the "injection site sarcoma", "injection site tumour","injection site cancer","-vaccine-associated sarcoma", "vaccine-associated tumour" and "vaccine-associated cancer", "foreign body sarcoma", "foreign body tumour", "foreign body cancer", "foreign body tumorigenesis", "microchip sarcoma", "microchip tumour" and "microchip cancer" search strings were used. Subsequently, the references of the selected publications were searched for further relevant literature.

IDENTIFIED LITERATURE

The relevant literature identified consisted mainly of case reports and case series describing a limited number of animals. The species for which literature was identified were: dogs (Jacobs, Poehlmann, et al., 2017), ferrets (Munday, Stedman, et al., 2003), a lion (Kinne and Tarello, 2007), a rabbit (Petterino, Modesto, et al., 2009) and a horse (Kannegieter, Schaaf, et al., 2010).

The dog is the most frequent species apart from cats for which suspected cases of ISS have been described. In 2003, Vascellari and colleagues described 15 cases of fibrosarcoma excised from where injections were thought to have been performed (Vascellari, Melchiotti, et al., 2003).In a later publication in 2006, Vascellari and colleagues described a case report of a dog with a fibrosarcoma in the back of the neck. The dog received several previous injections at this site, both for vaccinations and the placement of a microchip (Vascellari, Melchiotti, et al., 2006). In 2016, a case of extraskeletal osteosarcoma in the interscapular region in a dog was described (Selmic, Griffin, et al., 2016). The animal had received several injections at this site before. Jacobs et al. described a case of possible canine injection site sarcoma in 2017 (Jacobs, Poehlmann, et al., 2017).The dog developed tumours in the dorsocervical area after receiving injections at this site 3 weeks before.

In 2003, a retrospective case series of fibrosarcomas in ferrets was published (Munday, Stedman, et al., 2003). Seven of these fibrosarcomas occurred at a site regularly used for vaccinations.

In 2009, a case of interscapular fibrosarcoma in a rabbit was published (Petterino, Modesto, et al., 2009). The tumour developed at a site where several injections were performed. The authors stated that the histology of the tumour resembled that of a FISS.

A single case report of ISS in a horse was published in 2010 (Kannegieter, Schaaf, et al., 2010). This animal developed a fibrosarcoma 2 weeks after vaccination for equine influenza.

Finally, FISS has also been described in other fe-

line species than the domestic cat. In 2007, a case report of potential injection site sarcoma was described in a lion (Kinne and Tarello, 2007). The animal developed fibrosarcoma around 2 months after being vaccinated for feline leukaemia virus, feline rhinovirus and rabies. These authors also refer to a conference proceeding reporting a case of FISS in a tiger in 1998 (Kinne and Tarello, 2007). This publication was unfortunately not able to be sourced.

It is clear that the body of literature regarding ISS apart from the domestic cat is very limited as compared to literature about FISS. This supports the hypothesis that the condition is rare outside of the domestic cat. Other factors such as less reports and injection frequency in other species could also contribute to the smaller number of publications. It should also be noted that in most cases no assessment was performed to establish a causal relationship between an injection and the development of neoplastic disease. Additionally, almost all literature consists of case reports and case series describing a limited number of animals. Afinal observation is that a substantial amount of the identified literature regarding ISS apart from the domestic cat has been published more than 10 years ago.New research could provide important insights regarding potential changes in the incidence or characteristics of this condition.

CASE CHARACTERISTICS AND RISK FACTORS

The average age of cats affected by FISS was between 8 and 9 years in several studies (Hendrick, Shofer, et al., 1994; Doddy, Glickman, et al., 1996; Vascellari, Melchiotti, et al., 2003).The majority of FISS cases have been reportedto occur between 4 months and 3 years after injection (Hartmann, Day, et al., 2015). Fibrosarcomas are the most frequent kind of FISS(Doddy, Glickman, et al., 1996). In cats, it has been found that the risk of developing ISS does not vary between vaccine brands or manufacturers (Kass, Spangler, et al., 2003). The identified literature for ISS except that concerning the domestic cat was screened for several factors, including vaccine brand, age and injection site.

The dogs affected by potential ISS in the case series were on average 6.2 years old, but the age ranged from 7 months to 11 years (Vascellari, Melchiotti, et al., 2003). The animals in the case report were respectively 9, 6 and 11 years old (Vascellari, Melchiotti, et al., 2006; Selmic, Griffin, et al., 2016; Jacobs, Poehlmann, et al., 2017). In almost all of these cases, the presumed ISS was a fibrosarcoma, except for the 2016 case report (Selmic, Griffin, et al., 2016), where an osteosarcoma was diagnosed. Several breeds of dogs have been described that developed presumed ISS. In the case series (Vascellari, Melchiotti, et al., 2003), mixed breeds (6/15), Collie (1/15), German Shepherd (1/15), Schnauzer (1/15), Chow-Chow (1/15), Golden Retriever (1/15), American Pit Bull (1/15) Siberian Husky (1/15), Drahthaar (1/15) and Irish Setter (1/15) were reported. The case reports mention a French Bulldog (Vascellari, Melchiotti, et al., 2006), a Labrador (Selmic, Griffin, et al., 2016) and a Labrador Retriever(Jacobs, Poehlmann, et al., 2017). Based on these limited data, it is difficult to assess whether certain breeds have a predisposition to develop ISS. It is possible that this distribution is a normal variation or simply a reflection of the breeds that are usually kept. It is however apparent that the condition can develop in a wide variety of breeds. FISS has been estimated to occur in 1 - 10 of every 10,000 vaccinations in cats (Zabielska-Koczywąs, Wojtalewicz, et al., 2017). Because of the scarcity of the literature and the lack of epidemiological studies, it is difficult to assess the incidence of ISS in dogs. However, due to the widespread vaccination in dogs and the relative rarity of case reports in dogs as compared to cats, it can be hypothesized that the incidence in dogs is less than the incidence mentioned for FISS.

The age of the ferrets with sarcomas at an injection site in the study of Munday (Munday, Stedman, et al., 2003) ranged from 1 to 9 years. This study focused solely on fibrosarcomas. However, no literature regarding other sarcoma types at injection sites was identified for this species.

The dwarf rabbit in the 2009 case report was 1 year old when it received a vaccination (Petterino, Modesto, et al., 2009). However, when it developed a fibrosarcoma, it was already 8 years old.

The horse described in the case report of Kannegieter was 12 years old and a Quarterhorse x Arabian (Kannegieter, Schaaf, et al., 2010). It developed a fibrosarcoma.

The lion developing a fibrosarcoma was only 8 months old (Kinne and Tarello, 2007).

TREATMENT AND OUTCOME

FISS in the domestic cat is usually treated by surgical removal of the tumour, with wide margins.

If indicated, adjuvant treatment strategies such as radio- and chemotherapy can also be performed(Zabielska-Koczywąs, Wojtalewicz, et al., 2017). Despite treatment, frequent local recurrence has been described (Hartmann, Day, et al., 2015). Metastasis has also been described in several cases (Saba, 2017).

The samples of the 15 fibrosarcomas described by the group of Vascarelli (Vascellari, Melchiotti, et al., 2003) were obtained from dogs that underwent surgical removal of their tumour. It is not clear whether these animals received any additional therapy such as chemotherapy or radiation. The survival outcomes or the presence of metastatic disease were not reported. In the case report published in 2006, the tumour was surgically removed taking into account margins of 2 cm (Vascellari, Melchiotti, et al., 2006).The authors state that the dog was doing well and that there has been no sign of recurrence. The canine osteosarcoma described in 2016(Selmic, Griffin, et al., 2016) was initially surgically removed with wide margins. No metastasis was revealed at this time. A subsequent surgical site infection was treated with amikacin, followed by cefpodoxime proxetil and finally chloramphenicol after subsequent cultures. A carboplatin treatment was initiated to control microscopic metastases. During chemotherapy treatment, no metastases were identified. However, 1 month after the final cycle of chemotherapy, a suspected metastasis was identified in the right lung. Afterwards, a toceranib phosphate and cyclophosphamide treatment was initiated. Eighteen months after diagnosis, the animal presented with bone metastatic disease. Toceranib phosphate and cyclophosphamide treatment were discontinued. Afterwards, the animal was treated with fractioned radiotherapy. The animal was euthanised 20.5 months after diagnosis. The dog in the more recent case report (Jacobs, Poehlmann, et al., 2017) had a surgical removal of the tumour with margins of 3 cm. After 10 weeks, a recurrence of the tumour was noted. Lung metastasis was not present. A new surgical excision with 3 cm margins was carried out. Additionally, a three-days a week schedule of toceranib was started. No metastatic disease was noticed during this therapy. Fifty weeks after the first surgical removal, the same procedure had to be carried out for a third time due to a new recurrence, together with a continuation of the tyrosine kinase inhibitor therapy. The authors reported that the animal was still in remission almost 2 years after the diagnosis.

A multi-institutional retrospective study combining different treatment strategies in dogs could prove to be clinically useful if a large number of institutions participate and the inclusion criteria are not too strict, for example by allowing all FISS tumour types and treatment types.This way, a large number of cases can be assessed especially concerning relations between various treatment management strategies, quality of life after treatment and possible complications. A disadvantage of this kind of approach is that it is difficult to connect particular treatment strategies with survival outcome

The initial treatments for the ferrets in the case series of Munday and colleagues (Munday, Stedman, et al., 2003) were not detailed. It can however be assumed that the tumours were partially or completely surgically removed, since samples were available. Information about other therapies were not available. The authors report follow-up data for 3 of the animals that had fibrosarcoma at an injection site. One animal had a tumour recurrence 3 months after surgery and was euthanised. Two other animals did not have recurrence 8 and 12 months after surgery.

The fibrosarcoma in the rabbit in the case report of Petterino and colleagues (Petterino, Modesto, et al., 2009) was surgically removed with wide margins. After 2 months, the tumour recurred at the same site. The animal was subsequently euthanised.

The fibrosarcoma in the horse of the case report of Kinnegieter and colleagues (Kannegieter, Schaaf, et al., 2010) was surgically removed without radiotherapy or chemotherapy. No metastasis to lymph nodes or distant organs was identified. After 4 months, there was no recurrence of the tumour found.

In the case report by Kinneand Tarello (Kinne and Tarello, 2007), the lion was treated by surgical removal of the tumour. Despite radiotherapy being indicated, it was not performed due to practical considerations. The animal was later euthanised due to the poor prognosis. The time between diagnosis or treatment and death was not reported.

Due to the rarity of this disease in species outside of the domestic cat, it is unlikely that a clinical trial assessing treatment strategies will be feasible.
However, there is currently consensus that FISS should be treated with surgical removal. Based on the literature mentioned above, it seems that this treatment strategy is also the treatment of choice for ISS

in other species.

CONCLUSION

The literature regarding ISS outside of domesticated cats is very sparse. Despite this limited body of evidence, ISS has been described in dogs, ferrets, a rabbit, a horse and a lion. However, in most of these cases no assessment regarding a causal link between injections and the neoplasm was made. In general, treatment strategies of FISS and ISS in other species are similar. Based on the current literature, it seems that the benefits of the reasons for injection could outweigh the risk of developing ISS in all species. It should be noted, however, that this conclusion is based on a very limited amount of evidence. Further research should be performed to better understand the epidemiology, causes and risk factors of ISS in other species than the domestic cat and to discover optimal treatment strategies.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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