

FELINE INJECTION-SITE SARCOMA (FISS): LITERATURE REVIEW

Sarcoma de aplicação em felinos (SAF): revisão de literatura

Raphael G. da Silva*¹ ; Paulo R. Martin² ; Eduardo F. Bondan³ 

*Corresponding author: Rua Santo André, nº 48, Jardim Bela Vista,
Guarulhos, SP, Brasil. CEP: 07132-350.
E-mail: rp.grillo@hotmail.com

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Abstract

This review study analyzed the etiopathogenesis, epidemiology, biological behavior, diagnosis, treatment, and prevention of feline injection-site sarcomas (FISS), malignant neoplasms associated with subcutaneous or intramuscular injection sites. Although the etiology is not fully understood, intense chronic inflammatory processes combined with mutations in tumor suppressor genes are believed to play a central role in its pathogenesis. Fibrosarcoma is the most common histological subtype, characterized by highly infiltrative behavior and a high rate of local recurrence, resulting in a guarded prognosis. Diagnosis is based on histopathological evaluation and imaging techniques to detect metastases and support therapeutic planning. Surgical excision is the primary treatment; however, when performed alone, it is associated with high recurrence rates and a median survival time of four to six months. Therefore, combining surgery with adjuvant therapies such as electrochemotherapy, chemotherapy, and radiotherapy is essential to improve tumor control and clinical outcomes.

Keywords: Feline injection-site sarcoma. Fibrosarcoma. Feline neoplasms. Multimodal treatment. Veterinary oncology.

Resumo

Este trabalho de revisão analisou a etiopatogenia, epidemiologia, comportamento biológico, diagnóstico, tratamento e prevenção dos sarcomas de aplicação em felinos (SAF), neoplasias malignas

- 1 Doctor of Veterinary Medicine, master of Science, professor, Cruzeiro do Sul University, Department of Surgery, São Paulo, SP, Brazil.
- 2 Doctor of Veterinary Medicine, self-employed practitioner, specialist in Veterinary Surgery and Oncology, São Paulo, SP, Brazil.
- 3 Doctor of Veterinary Medicine, doctor of Philosophy, full professor, Cruzeiro do Sul University and Paulista University, department of Environmental and Experimental Pathology, São Paulo, SP, Brazil.



associadas a locais de injeções subcutâneas ou intramusculares. Embora a etiologia não esteja totalmente esclarecida, acredita-se que processos inflamatórios crônicos intensos, aliados a mutações em genes supressores tumorais, desempenhem papel central na patogênese. O fibrossarcoma é o subtipo mais frequente, apresentando comportamento altamente infiltrativo e elevada taxa de recidiva local, o que resulta em prognóstico reservado. O diagnóstico baseia-se na avaliação histopatológica e em exames de imagem para detecção de metástases e planejamento terapêutico. A excisão cirúrgica é o tratamento principal; entretanto, quando realizada isoladamente, está associada a altas taxas de recorrência e sobrevida média de quatro a seis meses. Dessa forma, a associação com terapias adjuvantes, como eletroquimioterapia, quimioterapia e radioterapia, é fundamental para melhorar o controle tumoral e os desfechos clínicos.

Palavras-chave: Sarcoma de aplicação felino. Fibrossarcoma. Neoplasias felinas. Tratamento multimodal. Oncologia veterinária.

Introduction

Feline injection-site sarcoma (FISS) is a malignant neoplasm that develops at sites previously subjected to subcutaneous or intramuscular injections. Initially, this condition was associated with the administration of certain vaccines and was therefore termed vaccine-associated sarcoma. However, this designation is no longer considered appropriate, as vaccines are not the only agents implicated in the development of this neoplasm (Buracco *et al.*, 2002; Kass *et al.*, 2003; Munday *et al.*, 2011; Martano *et al.*, 2012; Srivastav *et al.*, 2012; Bloch *et al.*, 2020).

Although the etiology of FISS has not been fully elucidated, evidence indicates that chronic and exacerbated inflammatory reactions at the injection site, combined with genetic factors, play a significant role in its pathogenesis (Malkin *et al.*, 1990; Kass *et al.*, 2003; Nambiar *et al.*, 2001). Recent reviews reinforce the multifactorial nature of FISS, highlighting the contribution of immunopathogenic mechanisms, individual risk factors, and aspects related to clinical management, all of which are essential for understanding the biological behavior of this neoplasm (Hartmann *et al.*, 2023).

In this context, current studies demonstrate that the tumor microenvironment exhibits marked involvement of immune system cells, particularly tumor-associated macrophages, whose high density has been correlated with increased tumor aggressiveness. These findings underscore the potential of these cells as prognostic markers and as promising targets for future immunomodulatory approaches (Gomes *et al.*, 2025).

The diagnosis of FISS is established through histopathological examination, with fibrosarcoma being the most frequently identified subtype. Surgical resection constitutes the primary treatment; however, when performed as a sole modality, it is associated with high rates of local recurrence (Hershey *et al.*, 2000; Ogilvie; Moore, 2001; Séguin, 2002). Therefore, in order to reduce recurrence and improve tumor control, adjuvant therapies such as chemotherapy, radiotherapy, and electrochemotherapy have been widely incorporated into routine veterinary practice (Martano *et al.*, 2012; Ferreira *et al.*, 2016; Almeida; Pimenta; Sena, 2021).

The objective of this study is to conduct a literature review on feline injection-site sarcomas, addressing aspects related to etiopathogenesis, epidemiology, biological behavior, diagnosis, therapeutic options, and prevention strategies.

Literature Review

Transitional zones between inflammatory granuloma and sarcoma can be identified in histological samples of certain FISS cases, suggesting that inflammation precedes the development of this neoplasm (Hendrick *et al.*, 1994). Initially, it was believed that only vaccines containing aluminum-based adjuvants were involved in the etiopathogenesis of FISS, as traces of this adjuvant were identified in biopsy samples, indicating a possible association between such vaccines and tumor development (Hendrick *et al.*, 1992; Madewell *et al.*, 2001; VAFSTF, 2005). However, more recent studies have demonstrated no significant difference between the use of recombinant and inactivated vaccines, suggesting that both may influence sarcoma development (Srivastav *et al.*, 2012; Bloch *et al.*, 2020).

Despite the recognized importance of the inflammatory response, it is not sufficient on its own to induce neoplastic transformation. Genetic factors, such as mutations and inactivation of tumor suppressor genes, appear to play a relevant role in the development of FISS (Malkin *et al.*, 1990; Nambiar *et al.*, 2001). In addition, evidence indicates that other factors, including the administration of long-acting antibiotics, nonsteroidal anti-inflammatory drugs, chemotherapeutic agents, as well as persistent inflammatory processes and repeated trauma, are also associated with the onset of this neoplasm (Buracco *et al.*, 2002; Kass *et al.*, 2003; Munday *et al.*, 2011; Martano *et al.*, 2012; Srivastav *et al.*, 2012).

It is estimated that, for every 10,000 vaccinated cats, between one and ten may develop FISS (Macy; Hendrick, 1996; VAFSTF, 2005). Although its incidence is low when compared to the number of animals subjected to multiple injections, FISS is characterized by a guarded prognosis and challenging treatment (Macy; Hendrick, 1996; VAFSTF, 2005). Cats between nine and eleven years of age are most frequently affected, with no reported breed or sex predisposition (Hershey *et al.*, 2000; Phelps *et al.*, 2011; Ferrari *et al.*, 2017; Müller; Kessler, 2018; Dobromylsky; Richards; Smith, 2021). The interval between injection and sarcoma development may range from two months to five years, with the appearance of a firm mass observed, on average, approximately eight months after administration (Hershey *et al.*, 2000; Madewell *et al.*, 2001; Kass *et al.*, 2003; Kliczkowska *et al.*, 2015).

Beginning in 1996, the Vaccine-Associated Feline Sarcoma Task Force established the distal pelvic and thoracic limbs as the preferred sites for vaccine administration in cats. This strategy aimed to facilitate the identification of vaccines with greater potential to induce FISS and to expand surgical therapeutic options, including limb amputation when indicated (Romatowski, 1997; Morrison; Starr; VAFSTF, 2001).

FISS is a soft tissue sarcoma induced by an inflammatory process and is characterized by more aggressive local behavior, higher likelihood of recurrence, and moderate metastatic rates compared to sarcomas without a history of local injections (Hendrick *et al.*, 1994; Martano *et al.*, 2012; Hartmann *et al.*, 2015). These neoplasms typically show slow progression, with progressive, expansive, and infiltrative local invasion (Bacon *et al.*, 2007; Carneiro *et al.*, 2019). Most tumors present a pseudocapsule formed by compression of the peritumoral connective tissue, which may adhere to adjacent structures or even contain neoplastic cells.

Invasion occurs between adjacent tissues in a pattern similar to “glove fingers,” which explains the high recurrence rates observed when surgical resection is performed as a sole treatment modality, despite being technically straightforward, since microscopic tumor extensions remain within surrounding tissues (Forrest *et al.*, 2000; Dennis *et al.*, 2011).

Clinically, FISS generally presents as solitary nodules or, less frequently, as diffuse masses, with solitary nodules being the most common presentation (Figure 1). These lesions have a firm consistency, are located in the cutaneous or subcutaneous tissue, and may or may not be adherent to deeper planes. In most cases, they are initially painless and may contain cystic areas within the mass. Ulcerated and necrotic regions may also be observed, particularly in larger or long-standing lesions (Bacon *et al.*, 2007; Dennis *et al.*, 2011; Liptak; Christensen, 2020).

Figure 1 – Wide range of clinical presentations of FISS. (a) and (b) Right flank; (c) Left pelvic limb; (d) Right pelvic limb



T Source: Silva *et al.* (2023).

Sarcoma is a malignant neoplasm of mesenchymal origin that may arise from different cell types. Although these tumors exhibit similar clinical behavior, they are traditionally classified according to their tissue of origin (Dennis *et al.*, 2011). Fibrosarcoma is the most frequently identified histological type in FISS (Carneiro *et al.*, 2019; Bloch *et al.*, 2020). However, other histological subtypes, including rhabdomyosarcomas, liposarcomas, leiomyosarcomas, neurofibrosarcomas, malignant fibrous histiocytomas, undifferentiated sarcomas, and myxosarcomas, have also been described (Kliczkowska *et al.*, 2015; Bloch *et al.*, 2020).

The histogenesis of sarcomas is complex, and even with the aid of immunohistochemistry, difficulties may arise in precisely determining the cell of origin (Sirri *et al.*, 2016). Due to these limitations, Dennis *et al.* (2011) suggested the adoption of broader terminology, such as soft tissue sarcomas or spindle cell tumors. Although histological distinction is morphologically relevant, its impact on therapeutic decision-making and prognosis has been questioned, since different cellular subtypes, despite distinct origins, tend to exhibit similar clinical behavior (Müller; Kessler, 2018; Dobromylsky; Richards; Smith, 2021; Liptak; Christensen, 2020).

Case series studies indicate that FISS frequently presents with a high histological grade, deep invasion of adjacent tissues, and a marked peri- and intratumoral inflammatory response, predominantly lymphocytic or lymphoplasmacytic. In addition, areas of necrosis, desmoplasia, and the presence of satellite nodules are common, features that contribute to the locally aggressive behavior of these neoplasms (Novaes *et al.*, 2024).

In cats, the histological classification of sarcomas has been adapted from the system used in dogs, taking into account three main parameters: degree of cellular differentiation, mitotic index, and presence of tumor necrosis. The sum of these criteria defines the tumor's histological grade (Dennis *et al.*, 2011; Avallone *et al.*, 2021). Due to the higher frequency of anaplasia, elevated mitotic rate, and extensive areas of necrosis, FISS tends to present with higher histological grades compared to sarcomas not associated with injection sites (Porcellato *et al.*, 2017; Almeida; Pimenta; Sena, 2021), resulting in greater biological aggressiveness and a poorer prognosis.

Recently, a modification of the grading system for FISS in cats has been proposed, maintaining the parameters of mitotic index and tumor necrosis while replacing the criterion of cellular differentiation with quantification of the inflammatory response, based on the number of inflammatory and

multinucleated cells. However, additional studies are still required to determine the actual impact of this modified approach on disease prognosis (Dobromylsky; Richards; Smith, 2021).

According to the Vaccine-Associated Feline Sarcoma Task Force, any nodule that develops at an injection site should be carefully monitored. Warning criteria include persistence of the mass for more than three months, a diameter greater than two centimeters, or an increase in size one month after administration (Romatowski, 1997; Morrison; Starr; VAFSTF, 2001; VAFSTF, 2005). These criteria are widely applied in clinical practice to guide early investigation of FISS.

Fine-needle aspiration cytology is considered a screening test, assisting in the identification of neoplastic lesions and in the differential diagnosis from abscesses, cysts, inflammatory processes, or granulomas (Bray; Polton, 2016; Liptak; Christensen, 2020; Almeida; Pimenta; Sena, 2021). However, studies indicate that only approximately 50 percent of FISS cases achieve a definitive diagnosis through this technique (Martano; Morello; Buracco, 2011). This limitation is related to the intense peritumoral inflammation, the presence of necrotic areas and fluid content that may compromise cytological interpretation, as well as the inability of the technique to precisely determine tumor histogenesis (Ogilvie; Moore, 2001; Kliczkowska *et al.*, 2015). In contrast, histopathological analysis allows detailed evaluation of the neoplasm, enabling diagnostic confirmation and determination of the degree of malignancy (Avallone *et al.*, 2021).

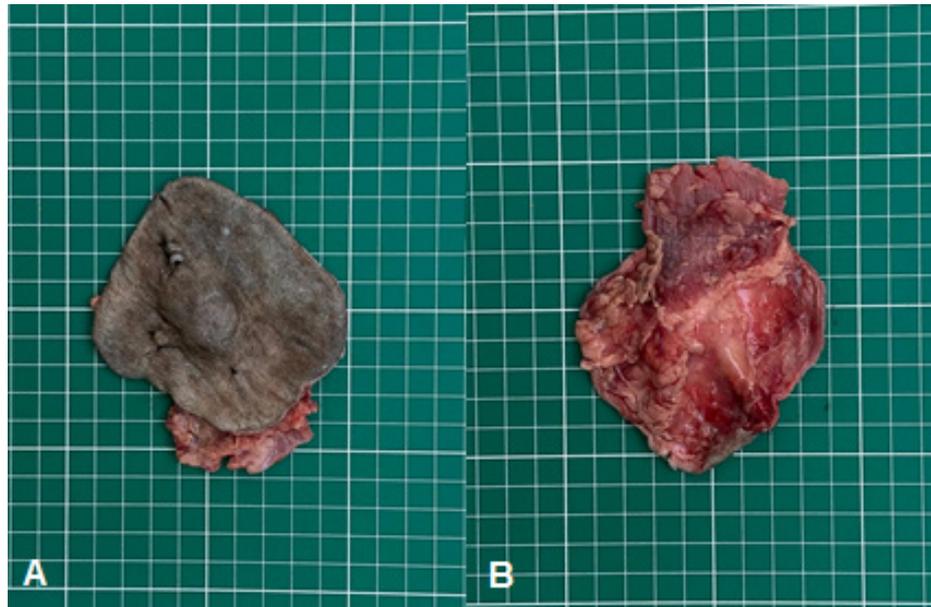
Imaging examinations, such as thoracic radiographs and abdominal ultrasonography, are indicated for the investigation of metastases, which occur in approximately 10 to 24 percent of cases. The lungs are the most frequently affected sites, followed by regional lymph nodes, skin, and liver (Hershey *et al.*, 2000; Ladlow, 2013). Computed tomography and magnetic resonance imaging are particularly useful for tumor staging, allowing more precise assessment of tumor extent and degree of infiltration, in addition to contributing to appropriate surgical planning (Travetti *et al.*, 2013; Zabielska-Koczywas; Wojtalewicz; Lechowski, 2017; Liptak; Christensen, 2020). Studies have demonstrated that measurement of FISS dimensions using these imaging modalities is superior to that obtained by manual palpation or calipers, reinforcing the need for their standardization during the clinical evaluation of these patients (Ferrari *et al.*, 2017; Fleming *et al.*, 2019).

Aggressive en bloc surgical resection of the neoplasm constitutes the main therapeutic modality for feline injection-site sarcomas (Phelps *et al.*, 2011). However, due to the high rates of local recurrence and limited survival observed when surgery is used as a sole treatment, a multimodal approach is recommended. This strategy combines surgical planning with adjuvant therapies, aiming to increase the disease-free interval and, consequently, prolong the survival of affected cats (Martano *et al.*, 2012; Ferreira *et al.*, 2016; Almeida; Pimenta; Sena, 2021).

Surgical excision should be performed with lateral margins of at least three to five centimeters and removal of at least two adjacent deep tissue planes (Figure 2). In many cases, this approach requires resection of structures such as ribs, vertebrae, or the scapula, as well as amputation of the affected limb when indicated (Ogilvie; Moore, 2001). Although the achievement of tumor-free surgical margins does not demonstrate a direct influence on overall survival time, it is associated with reduced local recurrence rates and prolonged disease-free intervals (Giudice *et al.*, 2010; Phelps *et al.*, 2011; Zabielska-Koczywas; Wojtalewicz; Lechowski, 2017; Müller; Kessler, 2018; Liptak; Christensen, 2020).

Despite the performance of wide-margin surgeries, recurrence rates remain high, ranging from 50 to 86 percent, typically within four to six months. This variation is related to factors such as tumor location, histological grade, and the experience of the surgeon performing the procedure (Hershey *et al.*, 2000; Poirier *et al.*, 2002; Séguin, 2002; Spugnini *et al.*, 2007; 2011).

Figure 2 – Removal of FISS with safety margins. (A) Lateral margins of 3 to 5 centimeters; (B) Adjacent deep tissue planes removed



T Source: Silva *et al.* (2023).

Chemotherapy constitutes a therapeutic option used both for palliative control and as adjuvant or neoadjuvant treatment of sarcomas, particularly those with a high histological grade (Hartmann *et al.*, 2015). Poirier *et al.* (2002) demonstrated a significant difference in time to tumor recurrence between animals treated exclusively with surgery and those that received chemotherapy as part of the therapeutic protocol. The combination of neoadjuvant chemotherapy with surgical resection resulted in an increased disease-free interval in the evaluated animals.

Administration of the chemotherapeutic agent prior to surgery promotes consolidation of the tumor pseudocapsule, facilitating greater drug penetration due to preservation of local microvascularization. In addition, tumor volume reduction is observed, allowing for wider surgical margins during resection (Bray; Polton, 2016).

Doxorubicin is the cytotoxic agent most frequently used in the treatment of FISS, owing to its superior therapeutic response and lower incidence of adverse effects compared to other available drugs (Ogilvie; Moore, 2001; Poirier *et al.*, 2002; Zabielska-Koczywas; Wojtalewicz; Lechowski, 2017). In cats, however, its use may be associated with side effects such as anemia, nephrotoxicity, and myelosuppression. Therefore, patients with renal insufficiency, hemolytic anemia, or autoimmune diseases present important restrictions regarding the use of this chemotherapeutic agent (Poirier *et al.*, 2002).

Radiotherapy may be employed either in the preoperative or postoperative period in the treatment of feline injection-site sarcomas. When used prior to surgery, its objective is to reduce tumor burden and eliminate neoplastic cells disseminated in adjacent tissues, thereby contributing to the achievement of more adequate surgical margins (Ladlow, 2013; Hartmann *et al.*, 2015). In the postoperative context, radiotherapy acts as a strategy to control possible residual cells, reducing local recurrence rates (Ladlow, 2013).

Patients undergoing combined surgical resection and radiotherapy demonstrate lower recurrence rates and longer disease-free intervals compared to those treated with surgery alone (Cohen *et al.*, 2001). However, this therapeutic modality is associated with relatively frequent adverse effects, including suture dehiscence, edema, seroma formation, cutaneous desquamation, alopecia, depigmentation, and, in some cases, signs of local infection (Cohen *et al.*, 2001; Bloch *et al.*, 2020).

The presence of metastases, large tumor volume, and a prolonged interval between surgical procedure and initiation of radiotherapy are associated with shorter survival times. These findings indicate that disease progression and early implementation of adjuvant treatment are determining factors for a more favorable prognosis (Bowl, 2015).

Electrochemotherapy consists of the combination of a physical method, characterized by the application of electrical pulses, with a chemical method involving the administration of chemotherapeutic agents (Spugnini *et al.*, 2008; Impellizeri *et al.*, 2016; Plaschke *et al.*, 2016). Exposure of cells to short, high-intensity electrical pulses induces transient alterations in the cell membrane, with reorganization of the lipid bilayer and formation of temporary hydrophilic pores, resulting in increased membrane permeability, a process known as electroporation (Giardino *et al.*, 2006; Impellizeri *et al.*, 2016).

Electroporation enables faster entry and higher intracellular concentrations of chemotherapeutic drugs within neoplastic cells, significantly enhancing their cytotoxicity (Cemazar *et al.*, 2008; Plaschke *et al.*, 2016). A relevant aspect of this technique is its cellular selectivity, as the adjacent connective tissue is preserved, reducing scar tissue formation and contributing to improved local structural preservation (Giardino *et al.*, 2006).

Studies indicate that the efficacy of electrochemotherapy in a single session is reduced in large nodules, making more than one therapeutic session necessary (Mali *et al.*, 2013; Plaschke *et al.*, 2016). Systemic adverse effects, such as hematological, muscular, cardiac, or renal alterations, are rarely reported. However, mild areas of local inflammation may occur, generally resolving spontaneously within two to three weeks (Spugnini *et al.*, 2007).

In cats with high-grade FISS undergoing combined surgical resection and electrochemotherapy, the interval to tumor recurrence ranged from twelve to twenty-two months, a value significantly higher than that observed in animals treated with surgery alone, in which recurrence occurred, on average, between four and six months (Spugnini *et al.*, 2007; 2011). The drugs indicated for electrochemotherapy must be hydrophilic, exhibit low cellular permeability, and possess high cytotoxicity. They may be administered intravenously or intratumorally in animals presenting with single or multiple neoplasms. Bleomycin is the chemotherapeutic agent most widely used in this therapeutic modality, as it meets these criteria and is associated with low rates of adverse effects (Mir, 2006; Spugnini *et al.*, 2017).

The prognosis of cats affected by injection-site sarcoma is variable and depends on multiple factors, including tumor location and size, histological grade, presence of metastases, choice of therapeutic protocol, and achievement of wide surgical margins, among other clinical and pathological aspects (Ladlow, 2013; Müller; Kessler, 2018; Gomes *et al.*, 2025). Animals that do not undergo any form of treatment have a mean survival time of approximately four months (Ladlow, 2013). In contrast, the best clinical outcomes have been observed when multimodal therapeutic approaches are adopted, combining surgical resection with adjuvant therapies such as electrochemotherapy, chemotherapy, and radiotherapy (Séguin, 2002; Bray; Polton, 2016).

With regard to prevention, the primary recommendation is to vaccinate cats only when indicated, in accordance with the guidelines established by the Vaccine-Associated Feline Sarcoma Task Force, as well as to avoid the administration of substances potentially associated with exacerbated inflammatory reactions (Romatowski, 1997; Morrison; Starr; VAFSTF, 2001; Hartmann *et al.*, 2015). Vaccination should be avoided in cats with a previous history of FISS, and, whenever possible, alternative routes of administration, such as oral or intravenous routes, should be considered. In addition, repeated multiple injections at the same site should be avoided, as these measures contribute to reducing the risk of developing this neoplasm (Ladlow, 2013).

The selection of injection sites that allow wide surgical resection, including the possibility of limb amputation, is also considered a relevant strategy to improve patient prognosis should FISS develop (Morrison; Starr; VAFSTF, 2001). Furthermore, studies indicate that the administration of vaccines at very low temperatures may be associated with an increased risk of FISS development, and it is therefore

recommended that immunobiological products be kept at room temperature for a few minutes prior to administration (Ladlow, 2013; Hartmann *et al.*, 2015).

Final Considerations

The prognosis of feline injection-site sarcomas remains guarded due to high local recurrence rates and the limited survival associated with this neoplasm. Early diagnosis, combined with wide-margin surgical resection and the use of adjuvant therapies, contributes to improved tumor control and prolonged disease-free intervals. In this context, it is essential to raise awareness among veterinarians regarding the need to balance the benefits of vaccination with the adoption of strategies that minimize the risks associated with the development of FISS. &

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