PESQUISA VETERINÁRIA BRASILEIRA
Brazilian Journal of Veterinary Research
ISSN 0100-736X (Print)
ISSN 1678-5150 (Online)

Pesq. Vet. Bras. 42:e07438, 2024
DOI: 10.1590/1678-5150-PVB-7438

Original Article
Small Animal Diseases

Feline application/inflammation-associated sarcoma: Gross aspects and histomorphological[1]

Vívian R.F. Novaes[2*], Angélica Consalter[3], Juliana S. Leite[2,4], Guilherme N. Souza[2,5], Thalita E.S. Oliveira[6], Simone C.S. Cunha[2] and Ana M.R. Ferreira[2,4]

ABSTRAT.- Novaes V.R.F., Consalter A., Leite J.S., Souza G.N., Oliveira T.E.S., Cunha S.C.S. & Ferreira A.M.R. 2024. **Feline application/inflammation-associated sarcoma: Gross aspects and histomorphological**. *Pesq. Vet. Bras. 44:e07438, 2024.* Veterinary Pathological Anatomy Laboratory, Faculty of Veterinary Medicine, Universidade Federal Fluminense, Rua Vital Brasil Filho, 64, Santa Rosa, Niterói, RJ 24230-340, Brazil. E-mail: vinovaes@id.uff.br

Feline injection-site sarcomas in felines account for more than 40% of cutaneous and subcutaneous neoplasms in felines. The present study aimed to describe the macroscopic and histomorphological findings of feline application/injection sarcomas. Samples from 31 feline tumors with a history of feline application/inflammation sarcoma were re-evaluated regarding histological subtype, mitotic index and score, depth of tissue invasion, and presence of inflammation considering the location, intensity and predominant cell types. Of the 31 samples from felines diagnosed with sarcoma at the application/inflammation site, 87.15% were cats with no defined breed (NDB), with a mean age of 8.5 years. The predominant anatomical sites were the back and flank/abdomen, both with 29% (9/31), and the prevalent histological subtype was fibrosarcoma at 77.4% (24/31), followed by anaplastic giant cell sarcoma at 12.9% (4/31) and myxosarcoma 9.6% (3/31). The histological grade with the highest number of cases was III (51.6%), followed by Grade II (35.4%) and I (12.9%). The mean of the longest axis measurements varied between the different tumor grades without being significant, with the average being 2.5±2.79cm in Grade I tumors and 3.2±2.28cm in Grade II tumors. and 4.68±2.07cm in Grade III tumors. Necrosis was observed in 74.2% of tumors. The tissue inflammation score was mild to moderate in 58% of cases and severe in 32.2%, with lymphocytic and lymphoplasmacytic infiltrates being prevalent, with 25.8% each, followed by lymphoplasmohistiocytic with 22.6%. The infiltration depth was 38.7% in muscle tissue, followed by 32.2% in the subcutaneous tissue. Pleomorphism was accentuated in 51.6%. Desmoplasia was moderate in 45.1%. Satellite nodules were present in 29% of cases, and 19.4% had macrophages with intracytoplasmic content suggestive of adjuvants. Surgical margins were infiltrated (M1) in 48.4% and narrowed in 25.8% (M2). The anatomical locations observed were different from those recommended by the Vaccine-Associated Feline Sarcoma Task Force (VAFST); in most cases, the adjuvanted macrophage was not present. From this data, we can suggest that sarcomas in felines are not only correlated to the vaccine

[1] Received on February 11, 2024.
Accepted for publication on March 6, 2024.

[2] Graduate Program in Veterinary Medicine in Animal Clinic and Reproduction, Universidade Federal Fluminense (UFF), Rua Miguel de Frias 9, Icaraí, Niterói, RJ 24220-900, Brazil.

[3] Hospital Universitário de Medicina Veterinária Professor Firmino Mársico Filho (HUVET), Faculdade de Veterinária, Universidade Federal Fluminense (UFF), Av. Almirante Ary Parreiras 503, Vital Brasil, Niterói, RJ 24230-321, Brazil.

[4] Laboratório de Patologia Clínica Veterinária, Departamento de Patologia e Clínica Veterinária, Universidade Federal Fluminense (UFF), Rua Miguel de Frias 9, Icaraí, Niterói, RJ 24220-900, Brazil.

[5] Embrapa Gado de Leite, Rua Eugênio do Nascimento 610, Juiz de Fora, MG 36038-330, Brazil.

[6] Departmento de Diagnóstico Histopatológico, VERUM Diagnóstico Veterinário, Rua Zacarias Costa Camargo 490, Lot. Remanso Campineiro, Hortolândia, SP 13184-310, Brazil. *Corresponding author: vinovaes@id.uff.br

application, corroborating the hypothesis that any material, whether liquid or solid, and any chronic inflammatory process in the subcutaneous tissue of cats can induce the entity if they are predisposed to do so. The detailed histomorphological data evaluated in this study were key points and provided important information about tumor behavior, being a tool for clinical-oncological decision-making.

INDEX TERMS: Histomorphological, inflammation feline sarcoma, histopathology, fibrosarcoma, cats.

INTRODUCTION

Application/inflammation-induced sarcomas in cats are aggressive tumors and account for >40% of skin and subcutaneous tissue neoplasms in cats (Kliczkowska et al. 2015). Specialists presume that these tumors occur due to the intense proliferation of fibroblasts and myofibroblasts in response to chronic inflammation in genetically predisposed animals. They may result from an inflammatory response secondary to the application of vaccines, surgical implants, and other administered drugs, as well as diseases that culminate in immunodeficiency (Dobromylskyj et al. 2020).

These tumors are malignant neoplasms of mesenchymal origin, classified as soft tissue sarcomas. Macroscopically, they appear firm, subcutaneous, or intramuscular, with irregular, single, diffuse, or multilobulated features. They are often white, with a cystic–necrotic center containing aqueous or mucinous fluids (Nitrini 2020). The tumors exhibit expansive growth and low metastatic potential (Martano et al. 2011, Nitrini 2020). The most common sites of sarcoma development are the subcutaneous tissue of the interscapular regions and the chest wall (Kliczkowska et al. 2015, Hendrick 2017). Morphologically, application/inflammation-induced sarcomas can vary and include fibrosarcoma, anaplastic giant cell sarcoma/malignant fibrous histiocytoma, and myxosarcoma (Couto et al. 2002). However, studies commonly classify them as fibrosarcomas (Esplin et al. 1993, Ferreira et al. 2016).

Moreover, the histological findings reveal a proliferation of myofibroblasts and giant cells, the presence of macrophages with yellowish phagocytic content, suggesting the presence of aluminum within them, as well as areas of central necrosis and peripheral granulomas (Couto et al. 2002). Additionally, there is abundant peripheral vascularization and predominantly lymphoid inflammation (Madewell et al. 2001, Couto et al. 2002).

Furthermore, the prognosis varies from poor to unfavorable, depending on the histopathological grade, tumor size, location, and resection with safety margins (Chalita & Reche 2003). In 1996, the Vaccine-Associated Feline Sarcoma Task Force (VAFST), aimed at minimizing the risks of this neoplasia, recommended administering vaccinations in the distal portion of the tail and limbs (Nóbrega et al. 2016, Saba 2017). The present study aimed to describe the macroscopic and histomorphological findings of sarcomas caused by applications/injections in cats, correlate them with histological grades and serve as a tool in determining the correct approach to clinical oncological treatments.

MATERIALS AND METHODS

Animal Ethics. The research protocol was approved by the Ethics Committee for the Use of Animals (CEUA) of "Universidade Federal Fluminense" (UFF), with approval number no. 5660060820 (ID 000962).

Data from 31 samples obtained from cats with a history of vaccine administration, medication, and chronic inflammation were reviewed. These samples underwent excisional biopsy at the UFF Veterinary Pathology Laboratory. Epidemiological data, including sex, age, anatomical location, and previous history, were obtained from the medical records.

Information on macroscopic aspects, measurements in centimeters (length, width, and thickness), shape and cut surface, location in the patient, presence or absence of ulceration, time of evolution, and disease progression from medical records and patient history were obtained. The histopathological changes and histological grades of the tumor were assessed following the classification proposed by Dobromylskyj et al. (2020), which includes three parameters: mitotic count (mitotic count in 10 fields at 40× magnification/FN 22/2.37mm^2), tissue necrosis score (absent, <50%, and >50%), and tissue inflammation score (absent/minimal, mild-to-moderate, and severe).

Additionally, other parameters were assessed, such as the depth of infiltration (dermis, subcutaneous, muscular, or combined), location of inflammation (peritumoral, intratumoral, or both), type of inflammation (lymphocytic, lymphoplasmacytic, or lymphoplasmacytic–histiocytic), pleomorphism (discrete, moderate, or marked), multinucleated cells (absent, rare, occasional, or prominent), desmoplasia (absent, mild, moderate, or marked), presence or absence of satellite nodules, ulceration, and macrophages with adjuvants.

The margins were evaluated as described by Stromberg & Meuten (2017), considering M1 = infiltrated margin (focally or diffuse), M2 = narrow margin (<2mm), M3 = clean margin (2-5mm), and M4 = clean margin (>5mm).

We coded the data obtained into Excel® tables and then processed them using the statistical program SPSS to evaluate the frequencies of diagnoses and histological variables observed in the neoplasms.

The Shapiro-Wilk test was used to assess the normal distribution of the response variables. ANOVA, a parametric test, was applied to variables with a normal distribution, whereas the Mann-Whitney test – a nonparametric test – was applied to variables with a 95% significance level.

RESULTS

Animals

Thirty-one animals were used in this study, with 17/31 (55%) being females and 14/31 (45%) males, with a mean age of 8.5 years. The predominant breed was mixed-breed, accounting for 27/31 (87.1%) of cats, followed by Persian with 2/31 (6.2%) and Brazilian Shorthair and British Shorthair, both with 3.35%. Anatomical locations included the back and flank/abdomen, both observed in 9/31 (29%) of cases, followed by the thorax in 5/31 (16.1%), pelvic limb in 3/31 (9.7%), ear in 2/31 (6.5%), thoracic limb in 1/31 (3.2%), and 2/31 (6.5%) in an unknown location (Table 1). Considering the cases with a clinical history (n=25), 80% (20/25) were post-vaccination, 8% (2/25) post-administration of liquid medication, 4% (1/20) post-microchip implant reaction, 4% (1/25) due to chronic inflammation in the ear pinna, and 1% (1/25) due to a reaction to the suture from elective castration surgery.

Macroscopic evaluation

The mean measurement of the longest axis of the nodules was 3.98cm, with the longest measuring 8.6cm and the shortest 0.6cm (Table 1). Ulceration was absent in 96.8% (30/31) of cases. When the nodule was cut, the consistency was firm in 11/31 (35.4%) of cases, fibroelastic in 10/31 (32.2%), and soft in 8/31 (25.8%). The coloration was white in 17/31 of cases (54.8%), light brown in 10/31 (32.2%), pink in 1/31 (3.2%), and uninformed in 3/31 (9.7%).

Histopathological evaluation

Fibrosarcoma (Fig.1-3) was the predominant histological subtype, accounting for 24/31 of cases (77.4%), followed by anaplastic giant cell sarcoma/malignant fibrous histiocytoma (Fig.4-5) with 4/31 (12.9%) and myxosarcoma with 3/31 (9.6%) (Fig.6). Additionally, two nodules showed an area of malignant osteoid differentiation.

Moreover, the most common histological grade was Grade III, accounting for 16/31 of cases (51.6%), followed by Grade II with 11/31 (35.4%) and Grade I with 4/31 (12.9%). Table 2 presents some characteristics separated into Grades I, II, and III. The mean measurements of the longest axis did not differ significantly among tumor grades, with values of 2.5±2.79cm, 3.2±2.28cm, and 4.68±2.07cm in Grade I, II, and III tumors, respectively.

Furthermore, fibrosarcoma was classified as Grade III in 11/23 (47.9%) of cases, Grade II in 9/23 (39.1%), and Grade I in 3/23 (13.0%). All cases of pleomorphic sarcoma were Grade III, including those with areas of transformation to osteosarcoma. Myxosarcoma accounted for 1/3 (33.3%) of cases across the three grades. Lastly, fibrosarcoma with areas of transformation into osteosarcoma was classified as Grade II.

The overall mean number of mitoses in an area of 2.37mm^2 was 24.5. The mitotic mean of fibrosarcoma was 23.87, anaplastic giant cell sarcoma was 26.75, myxosarcoma was 15.6, anaplastic giant cell sarcoma/fibrous histiocytoma with an area of transformation into osteosarcoma was 30, and fibrosarcoma with areas of transformation into osteosarcoma was four. Mitotic score 1 accounted for 6/31 of cases (19.35%), score 2 for 8/31 (25.8%), and score 3 for 17/31 (54.8%). In Grade I tumors, mitotic score 1 accounted for 75% of cases, whereas score 2 accounted for 25%. In Grade II tumors, mitotic

Table 1. Feline injection-site sarcoma according to anatomical location, size, and morphological diagnosis. Niterói, 2023

Case number	Anatomical location	Size (longest axis in cm)	Diagnosis*
1	B	1.3	1
2	T	8	1
3	AF	6.5	1
4	TM	NI	1
5	PL	4.5	4
6	T	8.6	1
7	B	8	1
8	B	6	2
9	AF	2.5	1
10	B	3.2	1
11	AF	5	1
12	T	2	1
13	AF	4.3	1
14	AF	2	5
15	AF	4.2	1
16	AF	8	1
17	T	3.5	1
18	B	NI	3
19	PL	1.5	3
20	NI	3	1
21	B	3	1
22	NI	1	1
23	B	4.5	2
24	E	3.5	1
25	T	1	1
26	AF	4	2
27	B	0.6	3
28	PL	5.8	1
29	B	2.5	1
30	AF	3.9	1
31	E	3.7	1

B = back, T = thorax, AF = flank/abdomen, PL = pelvic limb, TM = thoracic limb, E = ear, NI = not informed; * 1 = Fibrosarcoma, 2 = anaplastic sarcoma with giant cells, 3 = myxosarcoma, 4 = anaplastic sarcoma with giant cells with areas of transformation into osteosarcoma, 5 = fibrosarcoma with areas of transformation into osteosarcoma.

score 2 accounted for 54.5% of cases, whereas in Grade III tumors, mitotic score 3 accounted for 93.3% (Table 2).

Necrosis (Fig.7) was observed in 23/31 cases (74.2%) and was absent in 8/31 (25.8%), with <50% of the neoplastic area showing necrosis in 3/31 of cases (9.6%) and larger necrotic areas in 20/31 (64.5%). In Grade I tumors, necrosis was absent in 75% of cases. In Grade II tumors, necrosis was present in 91% of cases, with 63.7% exhibiting <50% necrosis. In Grade III tumors, 87.5% of cases exhibited necrosis, with 12.5% showing necrotic areas larger than 50% of the tumor (Table 2). The inflammation score (Fig.8) was minimal in 3/31 cases (9.6%), mild-to-moderate in 18/31 (58%), and severe in 10/31 (32.2%). Among Grade I tumors, 50% of cases showed minimal-to-moderate inflammation. In Grade II tumors, 63.7% of cases had a moderate inflammatory score. In Grade III tumors, 56.3% and 43.7% of cases exhibited moderate and severe scores, respectively (Table 2). Additionally, the most common type of inflammation was lymphoplasmacytic in 8/31 cases (25.8%), followed by lymphocytic in 8/31 (25.8%) and lymphoplasmacytic in 7/31 (22.6%). The inflammation was peritumoral in 5/31 of cases (16.1%), intratumoral in 6/31 (19.4%), and peri- and intratumoral in 20/31 (64.5%). Moreover, among the observed cases (N = 28), the depth of infiltration was as follows: 1/28 (3.6%) in the dermis, 10/31 (35.7%) in subcutaneous tissue, 12/28 (42.9%) in muscle tissue, 3/28 (10.6%) in the dermis and subcutaneous tissue, 1/28 (3.6%) in subcutaneous and muscular tissue, and 1/28 (3.6%) from dermis to muscular tissue. Multinucleated cells were prominent in 5/31 of cases (16.1%), occasional in 7/31 (22.6%), rare in 8/31 (25.8%), and absent in 11/31 (35.5%). Desmoplasia was moderate in 14/31 of cases (45.1%), mild in 10/31 (32.3%), and absent in 7/31 (22.6%). Satellite nodules were observed in 9/31 (29%) of the sarcomas (Fig.9), and 6/31 cases (19.4%) exhibited macrophages with adjuvants (Fig.10). Ulceration was present in only 2/31 cases (6.45%). Histological margins were infiltrated (M1) in most cases, accounting for 15/31 of cases (48.4%), followed by narrow margins (M2, <2mm) in 8/31 (25.8%), clean margins (M3, 2-5mm) in 3/31 (9.7%), and clean margins (M4, >5mm) in 5/31 cases (16.1%).

DISCUSSION

In this study, ulceration was absent in 96.8% of cases, an important macroscopic feature for clinicians. Fibrosarcoma was the predominant histological subtype in this study, consistent with several authors who have reported malignant fibroblast neoplasms as the most common in sarcomas induced by applications or inflammation (Doddy et al. 1996, Wilcock et al. 2012, Zanuncio et al. 2021, Pereira et al. 2021). The other

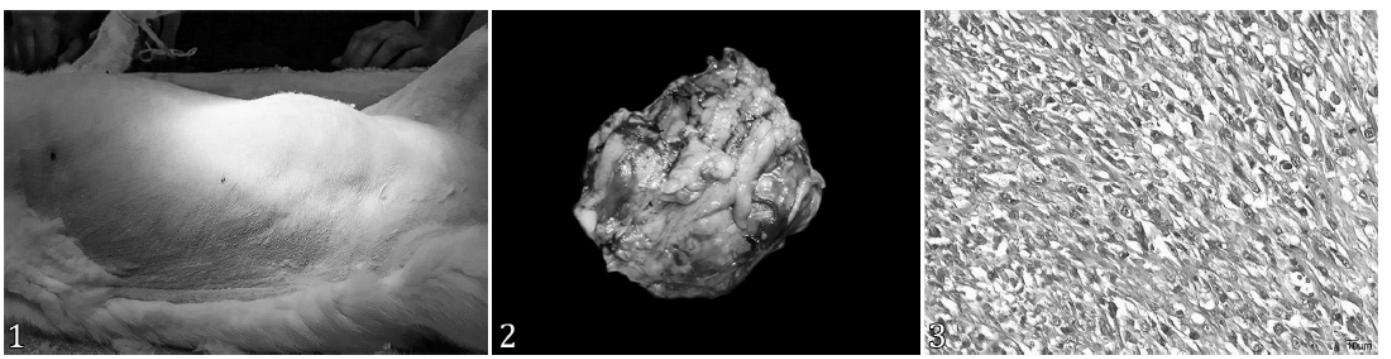

Fig.1-3. Macroscopy and microscopy of fibrosarcoma in a feline due to reaction to elective castration suture. (**1**) Anatomical location of the tumor mass in the abdomen. (**2**) Macroscopic image of fibrosarcoma. (**3**) Microscopic image of fibrosarcoma. Niterói, 2023. HE, obj.20x.

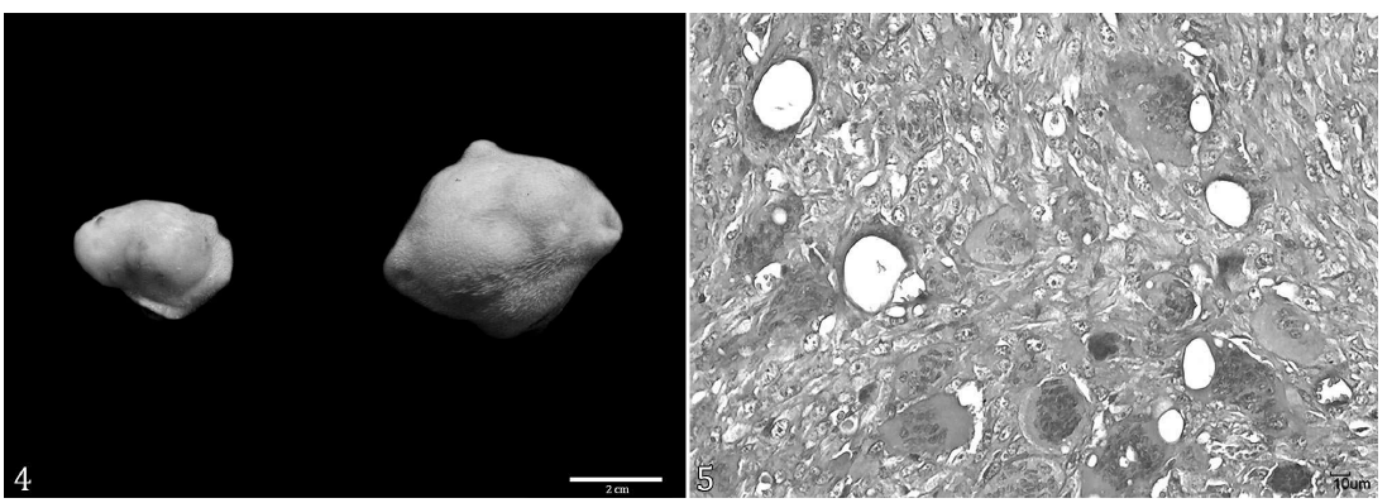

Fig.4-5. Macroscopy and microscopy of anaplastic giant cell sarcoma in a feline with a post-vaccination history. (**4**) Macroscopic image of anaplastic giant cell sarcoma. (**5**) Microscopic image of anaplastic giant cell sarcoma. Niterói, 2023. HE, obj.20x.

histological subtypes found in this study have also been documented in sarcomas caused by application by other authors (Couto et al. 2002, Esplin et al. 1993, Ferreira et al. 2016).

The anatomical locations varied among the back, flank, thorax, pelvic limb, thoracic limb, and ears, with the first two being the most prevalent. Kass et al. (1993) observed that 84% of feline application-induced sarcomas develop in the back, interscapular region. However, the anatomical locations observed in this study differed from those recommended by the VAFST, which suggests vaccination in the distal part of the tail and limbs (Nóbrega et al. 2016, Saba 2017). This discrepancy may partly indicate noncompliance with VAFST recommendations by veterinarians and may support a broader origin of the disease, given reports of sarcoma causes not correlated with vaccination (Hendrick & Brooks 1994, Buracco et al. 2002). Furthermore, it is noteworthy that the recommendations provided by VAST have been widely disseminated since their publication in 1999, and the present study included cases diagnosed from 2012 onward, with the period between application and sarcoma establishment ranging from three months to 10 years (Martano et al. 2005).

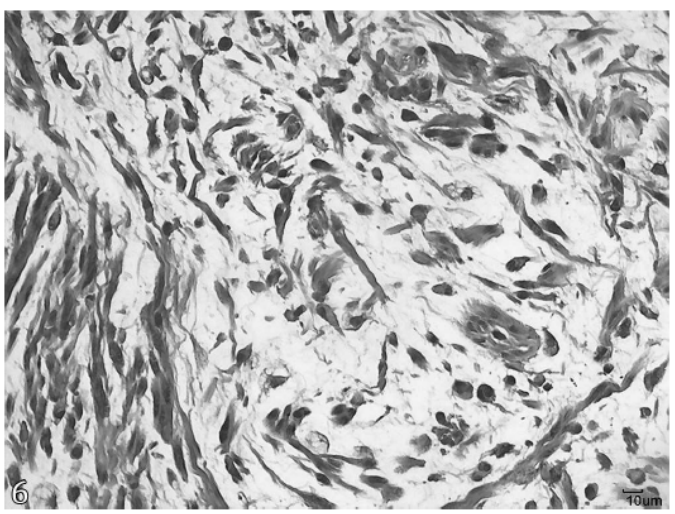

Fig.6. Microscopy of myxosarcoma in a feline with a post-vaccination history. Microscopic image of myxosarcoma. Niterói, 2023. HE, obj.20x.

Regarding the animals' age, the mean was 8.5 years, similar to the mean ages found by Doddy et al. (1996) and Pereira et al. (2021), suggesting that the disease affects elderly cats. Jelínek (2003) suggested that the higher prevalence of inflammation-induced sarcomas in elderly animals is due to the reactivity of the immune system in these animals. Regarding breed, the highest occurrence was in mixed-breed cats, corroborating the information found in the literature (Doddy et al. 1996, Rousset et al. 2013, Pereira et al. 2021), indicating that there is no predisposition regarding the breed and sex of the animals.

Moreover, the mean longest axis of the nodules was 3.98cm, similar to values reported in the literature (Rousset et al. 2013, Doddy et al. 1996, Pereira et al. 2021). Although the difference was not significant, the measurement of the longest axis tended to increase among the three histological grades, with a mean of 4.68cm observed in Grade III tumors, which could infer a worse prognosis in larger tumors. Moreover, studies report that sarcomas caused by injection are larger than noncorrelated sarcomas, and the correlation between size and prognosis remains controversial, leading to further studies. Doddy et al. (1996), when comparing fibrosarcoma correlated and not correlated to the application, suggested that sarcomas correlated to the application were more biologically aggressive, showing a higher growth rate and greater local invasion. Martano et al. (2005) suggested that tumors smaller than 4.0cm had better biological behavior, leading to better prognoses.

Table 2. Percentage of Grade I, II, and III tumors and respective indices of mitosis, necrosis, inflammatory score, multinucleated cells, and mean length of the longest axis. Niterói, 2023

		Tumor grading		
		I	II	III
Mitotic index	1	75%	27.2%	0
	2	25%	54.5%	6.7%
	3	0%	18.3%	93.3%
Necrosis	0	75%	27.3%	12.5%
	1	25%	63.7%	75%
	2	0%	9%	12.5%
Inflammation score	1	50%	9.00%	0%
	2	50%	63.7%	56.3%
	3	0%	27%	43.7%
Multinucleated cells	0	25%	50%	25%
	1	25%	20%	31.3%
	2	25%	30%	18.7%
	3	25%	0%	25%
Mean length of the longest axis (cm)	Mean	2.5 cm	3.2 cm	4.68 cm
	SD	2.79 cm	2.28 cm	2.07cm

Mitotic index: 1 = from 0 to 9 mitoses, 2 = from 10 to 19 mitoses, 3 = more than 19 mitoses; Necrosis: 0 = absence of necrosis, 1 = <50% necrosis, 2 = >50% necrosis; Inflammation: 1 = none, minimal, very mild, 2 = mild to moderate, 3 = severe; Multinucleated cells: 0 = absent, 1 = rare, 2 = occasional, 3 = frequent; SD = standard deviation.

Necrosis was observed in 74.2% of cases, with necrotic areas >50% of the tumor area in 64.51%. Zanuncio et al. (2021) found tumor necrosis in 94% of cases, with 37% having an area of necrosis >50% of the total area. Therefore, this difference may be correlated with the smaller average size of the largest axis they found (a mean of 3.0cm), suggesting a later diagnosis of the neoplasms in this study. Tumor necrosis is considered a predictor of poor prognosis in various neoplasms, as it can trigger persistent proinflammatory processes, inducing chronic inflammation and subjecting the host to constant exposure to proinflammatory cytokines (Yee & Li 2021).

The most common histological grade observed was Grade III, followed by Grades II and I. This finding corroborates the data reported by Zanuncio et al. (2021) and conflicts with those reported by Pereira et al. (2021), who found Grade II to be the most prevailing. In humans, the tumor grade of sarcomas is a predictive factor for prognosis and metastatic potential (Trojani et al. 1984). Fibrosarcoma cases were classified in all grades, with Grade III being the most prevalent. All cases of pleomorphic sarcoma were Grade III, including the one with areas of transformation to osteosarcoma.

Additionally, the overall mean number of mitoses in an area of 2.37mm^2 was 24.5. Porcellato et al. (2017) found a statistical difference in the mitotic score between animals without recurrence and those with tumor recurrence, suggesting that a number >20 in 10 fields of greatest increase may indicate an increased probability of recurrence and mortality. Moreover, similar studies have correlated higher mitotic scores with greater tumor progression and worse prognosis (Zanuncio et al. 2021, Pereira et al. 2021).

Peritumoral tissue inflammation was present in all tumors, similar to the findings reported by Couto et al. (2002) and Pereira et al. (2021). In this study, inflammation was moderate-to-severe in >90% of cases. Furthermore, no significant differences were observed between inflammatory distributions and types. Hendrick & Brooks (1994) suggested that the pathogenesis of sarcoma caused by inflammation involves the intense proliferation of fibroblasts and myofibroblasts in response to chronic inflammation. Couto et al. (2002) reported that activated neoplastic myofibroblasts form a barrier to the entry of T lymphocytes and macrophages, thus allowing tumor progression. According to Yee & Li (2021), the chronic inflammatory state can increase the chances of therapeutic complications and decrease the patient's tolerance to cancer therapies. Mikiewicz et al. (2023) concluded that inflammation plays a key role in tumor pathogenesis and progression and is directly proportional to sarcomas' tumor score and proliferative index.

Thus, no positive correlation was observed between the presence of multinucleated cells and tumor grade, which differs from the findings reported by Couto et al. (2002). In the present study, the presence of macrophages with adjuvants was <20%. Moreover, Kliczkowska et al. (2015) observed their occurrence in <50% of tumors. Therefore, vaccination is essential in felines and should not be interrupted due to the risk of developing sarcoma caused by applications/inflammation, as it is known that this pathology can result from a response to other associated injectable medical products (Hartmann et al. 2023).

CONCLUSION

Among the cases studied, fibrosarcoma was the predominant histological subtype. The measurements of the major axes were greater in higher-grade tumors. The anatomical locations observed differed from those recommended by the VAFST; in most cases, macrophages were not present with adjuvants. Consequently, we can suggest that sarcomas in cats are not solely correlated with vaccination, corroborating the hypothesis that any material, whether liquid or solid and any chronic inflammatory process in the subcutaneous tissue of cats can induce the disease, provided that they are predisposed to it.

Acknowledgments.- This study was funded by the "Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior" (CAPES), Brazil, "Conselho Nacional de Desenvolvimento Científico e Tecnológico" (CNPQ), "Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro" (FAPERJ) and the Veterinary Pathology Laboratory – UFF.

Conflict of interest statement.- The authors declare no conflicts of interest.

REFERENCES

Buracco P., Martano M., Morello E. & Ratto A. 2002. Vaccine-associated-like fibrosarcoma at the site of a deep nonabsorbable suture in a cat. Vet J. 163(1):105-107. <https://dx.doi.org/10.1053/tvjl.2001.0617> <PMid:11749145>

Chalita M.C.C. & Reche J.R.A. 2003. Fibrossarcoma, p.215-224. In: Souza H.J.M. (Ed.), Coletâneas em Medicina e Cirurgia Felina. Vol.1. L.F. Livros de Veterinária LTDA, Rio de Janeiro.

Couto S.S., Griffey S.M., Duarte P.C. & Madewell B.R. 2002. Feline vaccine-associated fibrosarcoma: morphologic distinctions. Vet. Pathol. 39(1):33-41. <https://dx.doi.org/10.1354/vp.39-1-33> <PMid:12102217>

Dobromylskyj M.J., Richards V. & Smith K.C. 2021. Prognostic factors and proposed grading system for cutaneous and subcutaneous soft tissue sarcomas in cats, based on a retrospective study. J. Feline Med. Surg. 23(2):168-174. <https://dx.doi.org/10.1177/1098612X20942393> <PMid:32713240>

Doddy F.D., Glickman L.T., Glickman N.W. & Janovitz E.B. 1996. Feline fibrosarcomas at vaccination sites and non-vaccination sites. J. Comp. Pathol. 114(2):165-174. <https://dx.doi.org/10.1016/s0021-9975(96)80005-3> <PMid:8920216>

Esplin D.G., McGill L.D., Meininger A.C. & Wilson S.R. 1993. Postvaccination sarcomas in cats. J. Am. Vet. Med. Assoc. 202(8):1245-1247. <PMid:8496079>

Ferreira M.G.P.A., Reis Filho N.P., Pascoli A.L.C.R., Storti R.P., Oliveira I.R.C. & Di Nardi A.B. 2016. Sarcoma de Aplicação em felinos: aspectos clínicos, diagnóstico e terapia. Revta Invest. 15(7):29-36.

Hartmann K., Egberink H., Möstl K., Addie D.D., Belák S., Boucraut-Baralon C., Frymus T., Lloret A., Hofmann-Lehmann R., Marsilio F., Pennisi M.G., Tasker S., Thiry E., Truyen U. & Hosie M.J. 2023. Feline injection-site sarcoma and other adverse reactions to vaccination in cats. Viruses 15(8):1708. <https://dx.doi.org/10.3390/v15081708> <PMid:37632050>

Hendrick M.J. & Brooks J.J. 1994. Postvaccinal sarcomas in the cat: histology and immunohistochemistry. Vet. Pathol. 31(1):126-129. <https://dx.doi.org/10.1177/030098589403100121> <PMid:8140720>

Hendrick M.J. 2017. Mesenchymal tumors of the skin and soft tissues, p.142-175. In: Meuten D.J. (Ed.), Tumors in Domestic Animals. 5th ed. John Wiley & Sons, Ames. <https://dx.doi.org/https://doi.org/10.1002/9781119181200.ch5>

Jelínek F. 2003. Postinflammatory sarcoma in cats. Exp. Toxicol. Pathol. 55(2/3):167-172. <https://dx.doi.org/10.1078/0940-2993-00307> <PMid:14620538>

Kass P.H., Barnes Jr. W.G., Spangler W.L., Chomel B.B. & Culbertson M.R. 1993. Epidemiologic evidence for a causal relation between vaccination and

fibrosarcoma tumorigenesis in cats. J. Am. Vet. Med. Assoc. 203(3):396-405. <PMid:8257557>

Kliczkowska K., Jankowska U., Jagielski D., Czopowicz M. & Sapierzyński R. 2015. Epidemiological and morphological analysis of feline injection site sarcomas. Pol. J. Vet. Sci. 18(2):313-322. <https://dx.doi.org/10.1515/pjvs-2015-0041> <PMid:26172181>

Madewell B.R., Griffey S.M., McEntee M.C., Leppert V.J. & Munn R.J. 2001. Feline vaccine-associated fibrosarcoma: an ultrastructural study of 20 tumors (1996-1999). Vet. Pathol. 38(2):196-202. <https://dx.doi.org/10.1354/vp.38-2-196> <PMid:11280376>

Martano M., Morello E. & Buracco P. 2011. Feline injection-site sarcoma: past, present and future perspectives. Vet. J. 188(2):136-141. <https://dx.doi.org/10.1016/j.tvjl.2010.04.025> <PMid:20510635>

Martano M., Morello E., Ughetto M., Iussich S., Petterino C., Cascio P. & Buracco P. 2005. Surgery alone versus surgery and doxorubicin for the treatment of feline injection-site sarcomas: a report on 69 cases. Vet. J. 170(1):84-90. <https://dx.doi.org/10.1016/j.tvjl.2004.04.004> <PMid:15993791>

Mikiewicz M., Paździor-Czapula K., Fiedorowicz J., Gesek M. & Otrocka-Domagała I. 2023. Metallothionein expression in feline injection site fibrosarcomas. BMC Vet. Res. 19(1):42. <https://dx.doi.org/10.1186/s12917-023-03604-5> <PMid:36759896>

Nitrini A. 2020. Sarcoma de aplicação felino: Revisão. Pubvet 15(01). <https://dx.doi.org/10.31533/pubvet.v15n01a738.1-12>

Nóbrega C., Mesquita J.R., Cruz R., Coelho C., Esteves F., Mega A.C., Santos C. & Vala H. 2016. Feline injection site sarcomas. Vet. Nurse 7(2):116-120. <https://dx.doi.org/10.12968/vetn.2016.7.2.116>

Pereira S.T., Gamba C.O., Horta R.S., Cunha R.M.C., Lavalle G.E., Cassali G.D. & Araújo R.B. 2021. Histomorphological and immunophenotypic characterization of feline injection site-associated sarcoma. Acta Scient. Vet. 49:1787. <https://dx.doi.org/10.22456/1679-9216.109525>

Porcellato I., Menchetti L., Brachelente C., Sforna M., Reginato A., Lepri E. & Mechelli L. 2017. Feline injection-site sarcoma: matrix remodeling and prognosis. Vet. Pathol. 54(2):204-211. <https://dx.doi.org/10.1177/0300985816677148> <PMid:28005492>

Rousset N., Holmes M.A., Caine A., Dobson J. & Herrtage M.E. 2013. Clinical and low-field MRI characteristics of injection site sarcoma in 19 cats. Vet. Radiol. Ultrasound 54(6):623-629. <https://dx.doi.org/10.1111/vru.12067> <PMid:23763538>

Saba C.F. 2017. Vaccine-associated feline sarcoma: current perspectives. Vet. Med., Res. Rep. 8:13-20. <https://dx.doi.org/10.2147/VMRR.S116556> <PMid:30050850>

Stromberg P.C. & Meuten D.J. 2017. Trimming tumors for diagnosis and prognosis, p.27-43. In: Meuten D.J. (Ed.), Tumors in Domestic Animals. 5th ed. John Wiley & Sons, Ames. <https://dx.doi.org/10.1002/9781119181200.ch2>

Trojani M., Contesso G., Coindre J.M., Rouesse J., Bui N.B., Mascarel A., Goussot J.F., David M., Bonichon F. & Lagarde C. 1984. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int. J. Cancer 33(1):37-42. <https://dx.doi.org/10.1002/ijc.2910330108> <PMid:6693192>

Wilcock B., Wilcock A. & Bottoms K. 2012. Feline postvaccinal sarcoma: 20 years later. Can. Vet. J. 53(4):430-434. <PMid:23024394>

Yee P.P. & Li W. 2021. Tumor necrosis: A synergistic consequence of metabolic stress and inflammation. BioEssays 43(7):e2100029. <https://dx.doi.org/10.1002/bies.202100029> <PMid:33998010>

Zanuncio V.V., Conceição L.G., Loures F.H., Cassali G.D., Rocha K. & Lima B.M. 2021. Hormone receptor expression, clinical and histopathological analysis in feline injection site sarcomas. Vet. Comp. Oncol. 19(3):473-481. <https://dx.doi.org/10.1111/vco.12666> <PMid:33211351>