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Histopathological characterization and analysis of cell proliferation in 162 cases of canine subcutaneous mast cell tumors in Brazil[1]

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ABSTRACT.- Jark P.C., Barros F.S., Apel T.L., Paula E.G., Xavier P.L.P., Garnica T.K., Ferrero A.T., Fukumasu H. & Sueiro F.A.R. 2024. **Histopathological characterization and analysis of cell proliferation in 162 cases of canine subcutaneous mast cell tumors in Brazil.** *Pesquisa Veterinária Brasileira 44:e07318, 2024.* Departamento de Clínica e Cirurgia Veterinária, Universidade Brasil, Av. Hilário da Silva Passos 950, Descalvado, SP 13690-000, Brazil. E-mail: paulocjark@hotmail.com

There are limited publications about canine subcutaneous mast cell tumors (MCT). International studies have shown that subcutaneous MCT has longer survival times than cutaneous MCT, with lower recurrence and metastasis rates. In addition, subcutaneous MCT has a specific histopathological classification (circumscribed, combined, or infiltrative pattern). Our study evaluated 162 cases of subcutaneous MCT diagnosed from 2014 to 2017 in Brazil. The mean age of the animals was 8.6 years, with a predominance of females and higher incidence in dogs with mixed breed (n=40), followed by Boxer (n=20), Labrador Retriever (n=14), Golden Retriever (n=11) and Pug (n=10). Regarding histopathological characterization, the most common infiltrative pattern represented 54.3% of cases, followed by circumscribed (34.8%) and combined (11%) patterns. The mean mitotic index (MI) was 1.04, with 93.9% of cases presenting MI≤4 and 53.1% MI=0. The data found in this Brazilian study regarding subcutaneous MCT does not differ from those described in American studies, suggesting similar genetic and epidemiological factors. The evaluated proliferation indices suggest that subcutaneous MCT presents slow progression and should be evaluated as a distinct form of cutaneous MCT.

INDEX TERMS: Canine subcutaneous mast cell tumor, epidemiology, prognosis, mitotic index.

RESUMO.- [**Caracterização histopatológica e análise de proliferação celular em 162 casos de mastocitoma subcutâneo em cães no Brasil.**] Há poucas informações prognósticas sobre o mastocitoma (MCT) subcutâneo em cães, apresentando maiores tempos de sobrevida e menores taxas de recidiva e metástase em comparação ao MCT cutâneo. Além disso, o MCT subcutâneo canino segue a classificação histopatológica própria, sendo subdivididos de acordo com o padrão em: circunscrito, combinado ou infiltrativo. Sendo assim, o principal objetivo desse estudo foi caracterizar a incidência e as características histopatológicas de MCT subcutâneos no Brasil. Para isso, foram avaliadas 164 amostras de MCT subcutâneos diagnosticados entre o período de 2014 a 2017 no Brasil. A média de idade dos animais foi de 8,6 anos (variação de 3 a 20 anos), com predomínio de fêmeas (64,8%) e maior incidência em cães sem raça definida (n=40), seguido de Boxer (n=20), Labrador Retriever (n=14), Golden retriever (n=11) e Pug (n=10). Em relação a caracterização histopatológica, o padrão infiltrativo foi o mais comum representando 54,3% dos casos, seguido dos padrões circunscritos (34,8%) e combinados (11%). Quanto

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a contagem de mitose (CM), 93,8% dos casos apresentam CM≤4 e, em 53,1%, CM=0. Os dados encontrados nesse estudo brasileiro em relação ao MCT subcutâneo reforçam outros trabalhos realizados em diferentes regiões demográficas, sugerindo fatores genéticos e epidemiológicos para a doença. Por fim, os índices de proliferação avaliados sugerem que o MCT subcutâneo apresenta progressão lenta devendo ser avaliado como uma forma distinta do MCT cutâneo.

TERMOS DE INDEXAÇÃO: Mastocitoma subcutâneo canino, epidemiologia, prognóstico, contagem de mitose.

INTRODUCTION

The majority of mast cell tumors (MCT) in dogs occur in cutaneous presentation. Although many MCTs originate in the dermis and invade the subcutaneous tissue, there is a specific presentation that is restricted to the subcutaneous tissue (Newman et al. 2007, Thompson et al. 2011a). The literature on cutaneous MCT is vast, but there is little information on subcutaneous MCT since, for a long time, this presentation of the disease was grouped with cutaneous MCT and classified as grade II due to subcutaneous infiltration (Newman et al. 2007, Thompson et al. 2011a, 2011b).

Subcutaneous MCTs are characterized by nodules of variable size surrounded by fatty tissue and are typically associated with slow growth rates. The distinction between subcutaneous MCT or cutaneous MCT with subcutaneous invasion is made exclusively by histopathological examination. The histopathological classification proposed for cutaneous MCTs that includes the Patnaik grading (grade I, II, and III) and recently, the Kiupel classification (high and low grade) cannot be applied to this subcutaneous MCT subgroup (Patnaik et al. 1984, Kiupel et al. 2011). According to Thompson et al. (2011a), the canine subcutaneous MCT is classified into three patterns: circumscribed, combined (infiltrative/circumscribed), and infiltrative.

The literature suggests that dogs affected by subcutaneous MCTs have longer survival times and lower recurrence and metastasis rates than those with cutaneous MCTs (Newman et al. 2007, Thompson et al. 2011a). Although for cutaneous MCT there are several clinical prognostic factors established in an attempt to predict the evolution of the disease, such as tumor size, growth rate, presence of ulceration, clinical staging, Patnaik grade, Kiupel grade, mitosis count, and immunohistochemical markers such as KIT and ki67. However, for subcutaneous MCT, these prognostic markers are still scarce (Patnaik et al. 1984, Kiupel et al. 2004, Webster et al. 2007, Blackwood et al. 2012).

There are few studies about canine subcutaneous MCT. Most of them were carried out in the USA, and there is no information to date regarding the incidence of these tumors and the histopathological characteristics of this neoplasm in Brazil and the exact characterization of the behavior of subcutaneous MCTs may be fundamental in establishing individualized treatments for according to the characteristics of the histopathological examination. Therefore, the main objective of this study was to characterize the incidence and histopathological characteristics of canine subcutaneous MCT in Brazil.

MATERIALS AND METHODS

Animal Ethics. This study was approved by the Animal Use Ethics Committee (CEUA) at the Descalvado campus of the "Faculdade de Medicina Veterinária" (College of Veterinary Medicine), "Universidade Brasil", under protocol number 011-17.

Selection of cases. The research was developed by evaluating a database from a partnership between the "Universidade Brasil" on the Descalvado campus and the VETPAT Laboratory in the city of Campinas. The information analyzed was exclusively about canine subcutaneous MCT, excluding other forms of the disease, such as cutaneous MCT, cutaneous MCT with subcutaneous invasion, or visceral forms of the disease. The patient's clinical data, such as breed, sex, age, size of the lesion, and histopathological diagnosis, were collected. The data were collected from January 2014 to July 2017.

Histopathological classification and determination of the mitotic index. Subcutaneous MCTs were classified according to Thompson et al. (2011a) in circumscribed, combined (infiltrative/circumscribed), and infiltrative. Furthermore, the mitosis count was determined by evaluating ten fields at 40x magnification. The animals were divided into two groups based on the number of mitotic figures (≤4 and >4) according to the cutoff factor previously established by Thompson et al. (2011a).

Statistical analysis. For statistical analysis, clinical data from dogs with subcutaneous MCT were analyzed by Spearman's non-parametric correlation test using the CORR procedure, SAS program, 9.3 (2012). The chi-square test and determination of adjusted standardized residuals were also used to observe associations between clinical data. Adjusted standardized residuals greater than 1.96 demonstrate an association between the variables.

Simple correspondence analysis (ANACOR). Correspondence analyses were performed using RStudio 4.3.1. Contingency tables were produced using the table or "sjt.xtab" function. Afterward, associations between variables using the chi-square test with k degrees of freedom followed by analyses of adjusted standardized residuals were carried out. The chi-square test evaluates whether the associations between the variable categories are given randomly or non-randomly, and to carry out the correspondence analysis, the associations must not be random (p<0.05). The coordinates of the perceptual map were determined through the decomposition of the total main Inertia, the formation of matrices from the "Row and Column profiles", followed by the extraction of eigenvalues demonstrating the number of dimensions captured by the analysis and the decomposition of the matrix values acquired. In short, categories located close together on the perceptual map have a greater association with each other.

RESULTS

A total of 164 subcutaneous MCT samples from 162 dogs were analyzed (two dogs presented two nodules). The average age of affected animals was 8.6 years (range 3-20 years). The most affected breeds were mixed breed dogs 40 (24.7%), Boxer 20 (12.3%), Labrador Retrievers 14 (8.6%), Golden Retrievers 11 (6.8%), and Pug 10 (6.2%). In total, 31 breeds were represented in this study. Regarding prevalence by sex, 105 (64.8%) females, 49 (30.2%) males, and in eight (4.9%) cases the sex was not specified (Fig.1).

Regarding the size of the lesions, 82 (50.6%) lesions were smaller than 3cm, 78 (48.1%) lesions were larger than 3cm, and in two (1.2%) cases, the size was not identified. Regarding the histopathological pattern of the cases analyzed, there

was a higher prevalence of MCT with an infiltrative pattern of 89 (54.3%), followed by circumscribed 57 (34.8%) and combined 18 (11%) (Fig.2).

Of the 44 cases of subcutaneous MCT that presented information regarding the surgical margin, 25 (56.8%) presented free margins, 11 (25%) compromised margins,

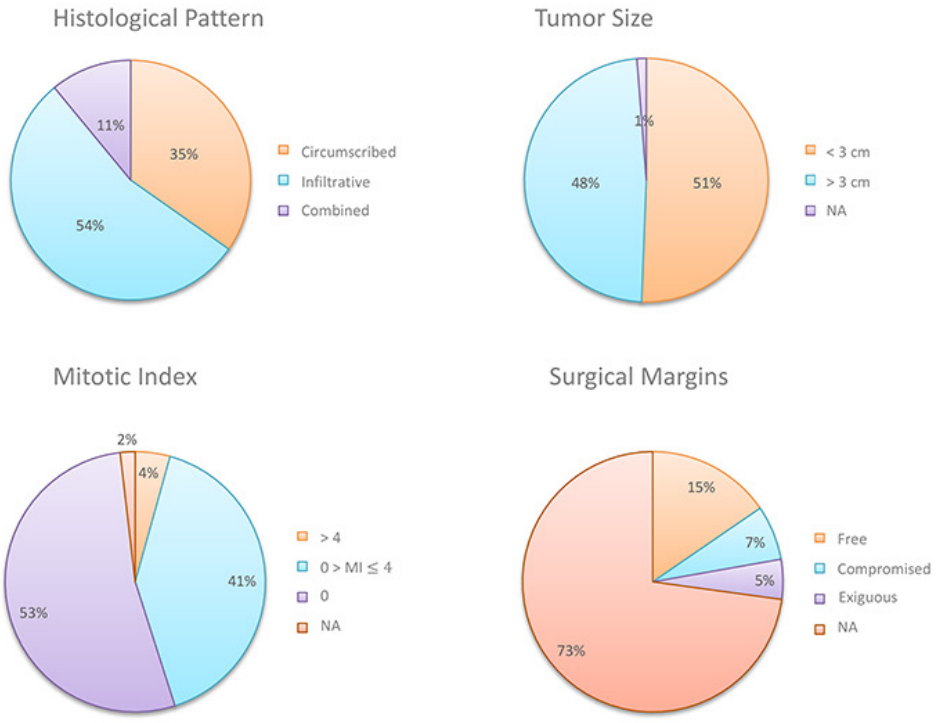

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Fig.1. Breed and sex distribution of canine subcutaneous mast cell tumors (MCT) cases in Brazil.

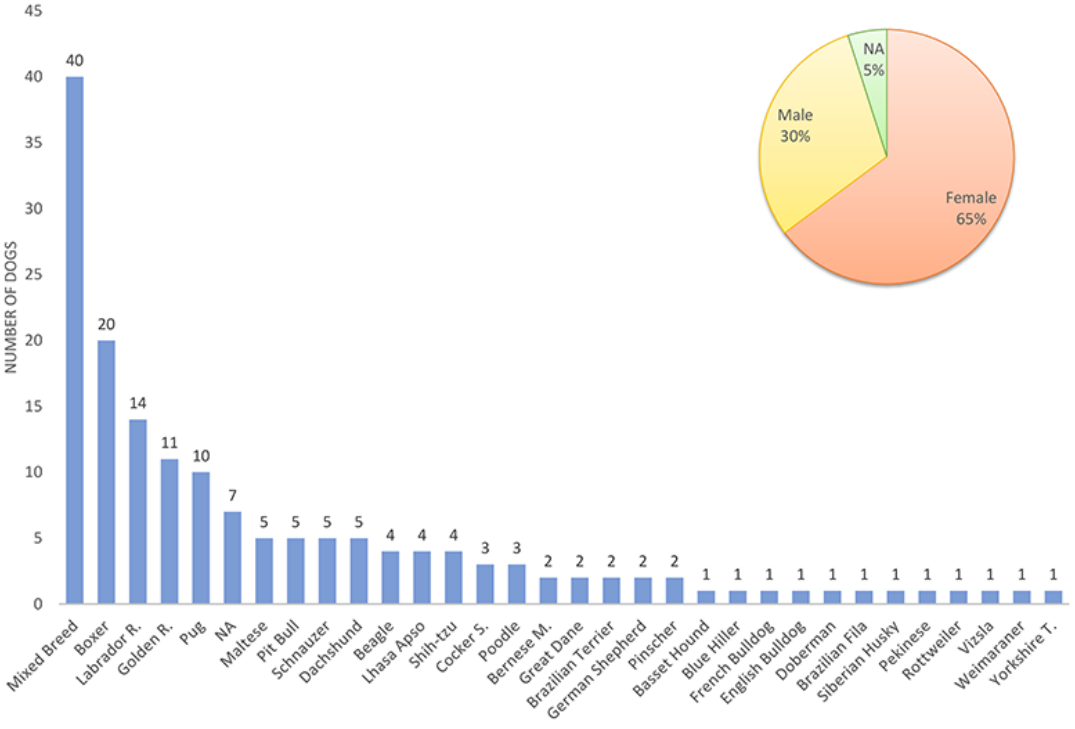

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Fig.2. Representation of Brazil's clinical and anatomopathological characteristics of canine subcutaneous mast cell tumors (MCT).

and eight (18.2%) narrow margins. Of the 25 cases with a free margin, 13 (52%) had a circumscribed pattern, seven (28%) had an infiltrative pattern, and five (20%) had a combined pattern. Of the eight cases with a small margin, six (75%) had an infiltrative pattern, and two (25%) had a circumscribed pattern. Of the 11 cases with compromised margins, nine cases (81.8%) were MCT with an infiltrative pattern, one (9.1%) with a circumscribed pattern, and one (9.1%) combined (Table 1).

The chi-square test and the analysis of adjusted standardized residuals (Fig.3) and correspondence analyses (Fig.4) demonstrated that there is an association between the histopathological pattern and surgical margin, with circumscribed subcutaneous MCTs being associated with free margins, while infiltrative subcutaneous MCTs are associated with compromised margins (chi-square = 11.862; *p*-value = 0.01841).

Table 1. Correlation of the histological pattern of 44 cases of subcutaneous mast cell tumor with surgical margin

Histological pattern	Surgical margin		
	Free	Exiguous	Compromised
Combined	5 (20%)	0 (0%)	1 (9.1%)
Circumscribed	13 (52%)	2 (25%)	1 (9.1%)
Infiltrative	7 (28%)	6 (75%)	9 (81.8%)
TOTAL	25	8	11

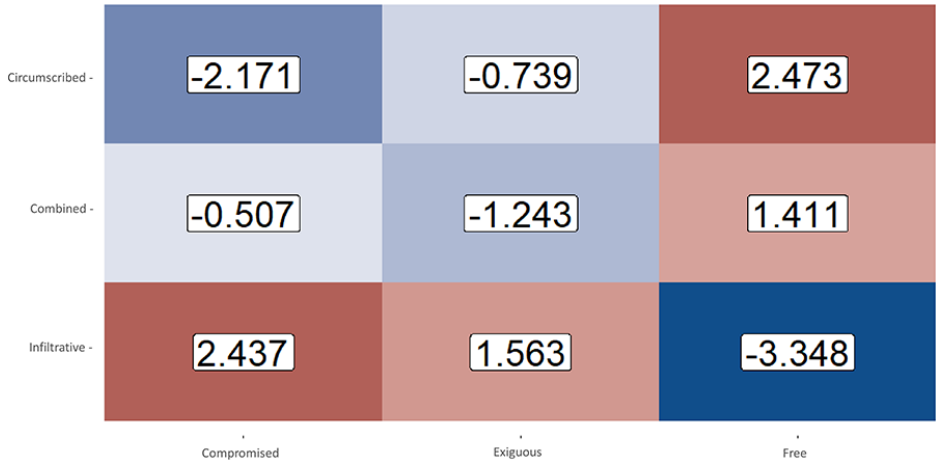

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Fig.3. Heat map displaying adjusted standardized residual values. There is an association between the categories of variables that present adjusted standardized residuals greater than 1.96.

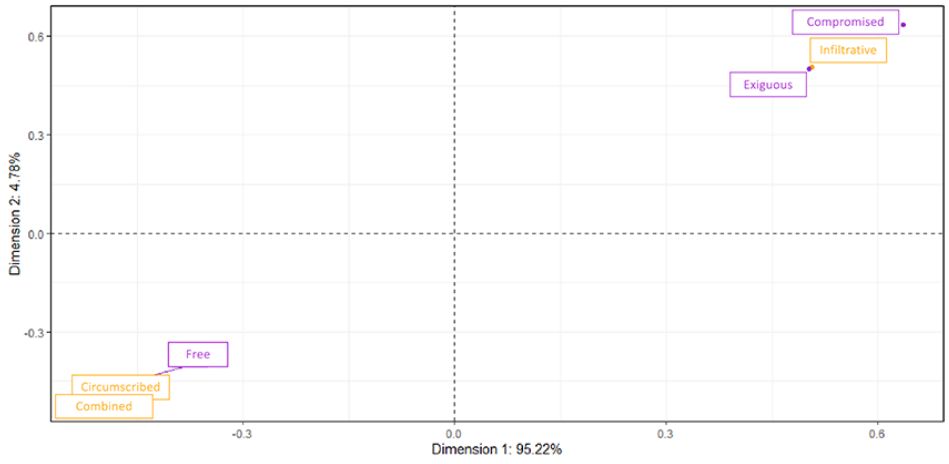

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Fig.4. Two-dimensional perceptual map from correspondence analysis demonstrating an association between infiltrative subcutaneous mast cell tumors (MCT) with compromised surgical margins and circumscribed subcutaneous MCT with free surgical margins.

Regarding the mitotic index (MI) of the evaluated subcutaneous MCT, 152 (93.8%) analyzed cases had MI≤4, seven (4.3%) cases had MI>4 (six infiltrative cases and one circumscribed case), and in three cases (1.9%) there was no information regarding the count of mitotic figures (Table 2). The overall mean MI of the 164 cases analyzed was 1.05 (range 0-18), with 53.1% presenting MI=0.

There was no strong correlation between the clinical characteristics of canine patients with subcutaneous MCT, mitosis count, and the histopathological classification pattern. There was a weak correlation (*p*-value between 0.3 and 0.4) between age and histopathological margin, lesion size and mitosis count, and mitosis count and histopathological margin. These analyses showed a positive correlation between older dogs with compromised surgical margins. A positive correlation was also between larger lesion sizes and higher mitosis counts. Finally, high mitosis count positively correlated with compromised surgical margin (Table 3).

DISCUSSION

The division of canine MCTs into cutaneous and subcutaneous can be considered recent in the literature since, for a long time, these tumors were grouped as a single disease. For this reason, there is little data in the literature about this specific form of MCT presentation in dogs, and there is no data in the Brazilian literature. The importance of characterizing subcutaneous MCT is because they are neoplasms that normally have a less aggressive evolution than cutaneous MCT and, therefore, must be treated with different approaches. For example, in a study by Thompson et al. (2011b) evaluating 306 cases of subcutaneous MCT, the recurrence and metastasis rates were considered low, representing 8% and 4%, respectively. In the present study, it was possible to carry out an epidemiological study and characterize the incidence and histopathological profile of subcutaneous MCT in Brazil, which is essential to alert veterinarians about the particularities of subcutaneous MCT and also to compare the findings of Brazilian studies with those found in other countries.

Regarding the breeds, age, and sex of the animals affected by subcutaneous MCT, the results found in the study follow those previously published in the literature. The most affected breeds were mixed breed dogs, Labrador Retrievers, Boxers, and Golden Retrievers, as in the study by Thompson et al. (2011a, 2011b). In another study evaluating 14 cases of subcutaneous MCT, Labrador retriever dogs were the most affected, with six cases (Da Silva et al. 2017). However, the suggestion that these breeds are the most affected by subcutaneous MCT may be influenced by the fact that they are extremely common breeds in the aforementioned countries. Therefore, further research evaluating the total population of dogs and the relative risk of developing subcutaneous MCT is necessary to confirm these findings.

The average age of the animals in the study by Thompson et al. (2011a) was eight years and two months, similar to the data found in the present study, in which the average age was 8.6 years. The predominance of females over males was also evidenced in the study by Thompson et al. (2011a).

As for the histopathological pattern, the most frequently found was infiltrative (54.3%), followed by circumscribed (34.8%) and combined (11%). In the study by Thompson et al. (2011b), the most common histopathological pattern was also infiltrative (50%), followed by combined (29.4%) and circumscribed (17.3%). The infiltrative histopathological pattern in both studies represents approximately half of the cases of subcutaneous MCT, suggesting that this is the predominant histological type in subcutaneous MCT.

Only 44 samples analyzed in the present study presented details about the surgical margin, and the majority were free or exiguous (20.4%), with only 6.8% of the margins analyzed being compromised. Of these, 81.8% were infiltrative MCT. In the case of circumscribed subcutaneous MCT, only one case had a compromised margin. When evaluating these data, it is suggested that the number of samples with free margins is greater in the circumscribed pattern, confirming the characteristic of this neoplasm of being less invasive and with a greater probability of being completely excised since histologically it is encapsulated, unlike the infiltrative pattern in which the challenge of obtaining a surgical margin is greater. Despite the possibility of compromised margins, the study by Thompson et al. (2011b) demonstrated that only 12% of tumors with compromised margins had recurrence, a much lower percentage than grade II cutaneous MCT with incomplete excision in which 23% of cases treated with surgery alone had disease recurrence.

Table 2. Correlation of the mitotic index with the histological pattern of 162 cases of canine subcutaneous mast cell tumor

Mitotic index	Histological pattern		
	Combined	Circumscribed	Infiltrative
≤4	18 (100%)	55 (98.2%)	80 (93.0%)
>4	0 (0%)	1 (1.8%)	6 (7.0%)
Total	18	56	86

Table 3. Non-parametric Spearman correlations, using the CORR procedure

Correlated parameters	Correlation analysis	
	ρ^2	Prob>$\|\rho\|^2$
Sex X Mitotic index	-0.1320	0.0103
Age X Histological pattern	0.2363	0.0066
Age X Surgical margin	0.3317	0.481
Tumor size X Mitotic index	0.3358	<.0001
Mitotic index X Surgical margin	0.3770	0.0117

One of the hypotheses raised in this same study by Thompson et al. (2011b) the reason why subcutaneous MCTs are less locally relapsing is that peritumoral adipose tissue release adipokines that can alter the behavior of subcutaneous MCTs, making them less aggressive locally. Another theory proposed by Thompson et al. (2011b) to explain the low recurrence rate, even in subcutaneous MCT with incomplete margins, focuses on the healing process of the site after surgery. The recruitment of inflammatory cells combined with the release of inflammatory cytokines and changes in the vasculature at the site of tumor excision may play an important role in the death of remaining neoplastic cells. Furthermore, the heterogeneity of neoplastic cells in subcutaneous MCTs would mean that cells in the periphery would not be able to sustain their survival as much as cells in the center of the tumor, leading to low rates of local recurrence, even in compromised margins (Thompson et al. 2011b). This is also seen in cutaneous mast cell tumors and other tumors, such as soft tissue sarcomas. In the study by Marconato et al. (2020), 19.4% of cutaneous mast cell tumors were removed with incomplete surgical margins, and no patient had local recurrence. In contrast, in the study by Chiti et al. (2021) with soft tissue sarcomas, it was found that despite the risk of recurrence in animals with compromised margins being 6.16 times higher compared to free margins, only 41.2% of patients with soft tissue sarcomas and compromised margins presented recurrence.

Concerning the various prognostic factors normally described in veterinary oncology, the mitosis count represents an independent factor in several neoplasms. MI becomes an important parameter in the histopathological evaluation of cutaneous and subcutaneous MCT, being correlated with an increase in the probability of the appearance of metastasis, recurrences (both local and distant), and a reduction in survival time, the higher the values of this index (Romansik et al. 2007, Elston et al. 2009).

The average MI value of the 164 cases analyzed was 1.05 lower than that found by Thompson et al. (2011a), which was 3.9. In this previously described study, dogs with MI>4 had significantly shorter survival times and shorter time to local recurrence and metastasis than dogs with MI<4. As in the study by Thompson et al. (2011a), 93.8% of the cases presented MI≤4, considered low according to the methodology described in the characterization of MI in subcutaneous MCT. Another interesting fact is that 53.1% of cases with MI=0, a result similar to that of Thompson et al. (2011a), in which 60% of the samples analyzed did not present mitotic figures, emphasizing the less aggressive behavior of this MCT presentation. Although the study by Thompson et al. (2011b) did not observe a correlation between MI and histological pattern, in the present study, six of the seven cases with MI>4 were of an infiltrative pattern, considered more aggressive among subcutaneous MCT.

CONCLUSION

Our results suggest that Brazil's predominant histological type of subcutaneous mast cell tumors (MCT) is infiltrative, representing more than half of the cases. Furthermore, our results suggest that there is an association between infiltrative subcutaneous MCT and the presence of compromised margins. In contrast, circumscribed subcutaneous MCT is associated with free surgical margins. Finally, canine subcutaneous MCTs showed a low mitosis count, suggesting a less aggressive behavior.

Conflict of interest statement.- The authors declare that there are no conflicts of interest.

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