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

Pesq. Vet. Bras. 43:e07124, 2023
DOI: 10.1590/1678-5150-PVB-7124

Original Article
Small Animal Diseases

Epidemiological, anatomopathological, and immunophenotypical aspects of cutaneous lymphomas in dogs[1]

Renata D. Mazaro[2], Douglas M. Lorenzetti[2], Suzana M.G. Leite[3], Eduardo K. Masuda[4], Leonardo D. Da Costa[5], Rosemeri O. Vasconcelos[6], Antonio Flávio M. Dantas[7], Luciana C. Lacerda[8], Tereza Cristina Da Silva[9], Marco Aurélio A. Motta[10], Bruno Cogliati[9] and Rafael A. Fighera[11]*

ABSTRACT.- Mazaro R.D., Lorenzetti D.M., Leite S.M.G., Masuda E.K., Da Costa L.D., Vasconcelos R.O., Dantas A.F.M., Lacerda L.C., Da Silva T.C., Motta M.A.A., Cogliati B. & Fighera R.A. 2023. **Epidemiological, anatomopathological, and immunophenotypical aspects of cutaneous lymphomas in dogs.** *Pesquisa Veterinária Brasileira 43:e07124, 2023*. Departamento de Patologia, Universidade Federal de Santa Maria, Av. Roraima 1000, Santa Maria, RS 97105-900, Brazil. E-mail: anemiaveterinaria@yahoo.com.br

Cutaneous lymphomas are uncommon tumors in dogs that can occur as epitheliotropic and non-epitheliotropic types. The epitheliotropic type comprises three, already well established, distinct clinicopathological presentations. However, the non-epitheliotropic lymphoma, despite its poor characterization, represents a heterogeneous group of not yet correlated presentations that can mimic different skin tumors, configuring a diagnostic challenge. Therefore, this study's main aim was to establish whether there is a correlation between the macroscopic presentation and the histological subtypes of cutaneous non-epitheliotropic lymphoma in the population of dogs involved in this study. Additionally, we aimed to determine the prevalence of each type and histological subtype of canine cutaneous lymphoma and describe the epidemiological and anatomopathological characteristics of the presented cases. From a total of 38 cases of cutaneous lymphoma diagnosed in dogs, 17 (44.7%) were considered as epitheliotropic and 21 (55.3%) as non-epitheliotropic. From the 17 cases of cutaneous epitheliotropic lymphoma, 13 (34.2%) and four (10.5%) were subclassified as mycosis fungoides and pagetoid reticulosis, respectively. The cases of cutaneous non-epitheliotropic lymphoma included were: anaplastic large T-cell lymphoma (ALTCL – 9/21, 23.9%), peripheral T-cell lymphoma, unspecified (PTCL-NOS – 4/21, 10.5%), subcutaneous panniculitis-like T-cell lymphoma (SPTCL – 4/21, 10.5%), diffuse large B-cell lymphoma – immunoblastic type (DLBCL – 2/21, 5.2%), lymphomatoid granulomatosis (LYG – 1/21, 2.6%), and marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT) - lymphoplasmacytic

[1] Received on July 24, 2022.
Accepted for publication on August 8, 2022.

[2] Programa de Pós-graduação em Medicina Veterinária, área de concentração em Patologia e Patologia Clínica Veterinária, Centro de Ciências Rurais (CCR), Universidade Federal de Santa Maria (UFSM), Av. Roraima 1000, Camobi, Santa Maria, RS, 97105-900, Brazil.

[3] Veterinarian, Rua Conde de Irajá 420, Botafogo, Rio de Janeiro, RJ 22271-020, Brazil.

[4] Axys Análises – Diagnóstico Veterinário e Consultoria Ltda., Rua Alberto Silva 332, Vila Ipiranga, Porto Alegre, RS 91370-000, Brazil.

[5] Veterinarian, Rua Bolívia 575, São Pedro, Belo Horizonte, MG 30330-360, Brazil.

[6] Laboratório de Histopatologia Veterinária (LHV), Faculdade de Ciências Agrárias e Veterinárias, Departamento de Patologia, Reprodução e Saúde Única, Universidade Estadual Paulista "Júlio de Mesquita Filho" (Unesp), Via de Acesso Prof. Paulo Donato s/n, Jaboticabal, SP 14884-900, Brazil.

[7] Laboratório de Patologia Animal (LPA), Hospital Veterinário Universitário, Centro de Saúde e Tecnologia Rural (CSTR),Universidade Federal de Campina Grande (UFCG), Av. Universitária s/n, Santa Cecília, Patos, PB 58708-110, Brazil.

[8] Célula – Laboratório Veterinário, Rua Castro Alves 398, Centro, Eunápolis, BA 45820-350, Brazil.

[9] Laboratório de Patologia Morfológica e Molecular (LAPMOL), Faculdade de Medicina Veterinária e Zootecnia (FMVZ), Universidade de São Paulo (USP), Avenida Prof. Dr. Orlando Marques de Paiva 87, Cidade Universitária, Butantã, São Paulo, SP 05508-270, Brazil.

[10] Centro Clínico e Cirúrgico Veterinário (CCCV), Rua Gonçalves Chaves 4806, Centro, Pelotas, RS 96015-560, Brazil.

[11] Departamento de Patologia, Centro de Ciências da Saúde, Universidade Federal de Santa Maria (UFSM), Av. Roraima 1000, Camobi, Santa Maria, RS 97105-900, Brazil. *Corresponding author: anemiaveterinaria@yahoo.com.br

variant (1/21, 2.6%). Based on the anatomopathological findings, it was possible to infer that when faced with multiple, nodular or placoid skin lesions, predominantly on the trunk and limbs, the diagnosis is more likely to be consistent with ALTCL. Whereas, with solitary skin nodules or plaques, PTCL-NOS will be the most frequently observed histological type. When these lesions are exclusively located in the subcutaneous tissue, one should first think about SPTCL and, more rarely, DLBCL. Regarding to epitheliotropic cutaneous lymphomas, the most commonly observed type in dogs is the cutaneous form of mycosis fungoides, especially in the pre-mycotic and mycotic phases. We hope that this information can assist veterinary clinicians and pathologists in their diagnostic routines and contribute to the characterization of non-epitheliotropic cutaneous lymphomas in the canine species.

INDEX TERMS: Skin lymphomas, cutaneous tumors, uncommon lymphomas, dermatopathology, dogs.

RESUMO.- [**Aspectos epidemiológicos, anatomopatológicos e imunofenotípicos dos linfomas cutâneos em cães.**] Linfomas cutâneos são tumores incomuns em cães que podem ocorrer sob as formas epiteliotrópica e não epiteliotrópica. A forma epiteliotrópica compreende três apresentações clinicopatológicas distintas já bem estabelecidas. Contudo, a forma não epiteliotrópica, apesar de ser reconhecida, é menos caracterizada, representando um grupo heterogêneo de apresentações ainda não correlatas e que aparentemente podem mimetizar diferentes tumores de pele, configurando um desafio diagnóstico. Assim, o objetivo principal deste trabalho foi tentar estabelecer se há correlação entre a apresentação macroscópica e os subtipos histológicos de linfoma cutâneo não epiteliotrópico da população de cães em estudo. Adicionalmente, objetivou-se determinar a prevalência de cada tipo e subtipo histológico de linfoma cutâneo canino, e ainda, descrever as características epidemiológicas e anatomopatológicas dos casos. Foram incluídos 38 casos de linfomas cutâneos caninos, desses, 17 (44,7%) eram epiteliotrópicos e 21 (55,3%) eram não epiteliotrópicos. Dos 17 casos de linfomas epiteliotrópicos, 13 (34,2%) foram subclassificados como micose fungoide e quatro (10,5%) como reticulose pagetoide. Os casos de linfomas cutâneos não epiteliotrópicos foram subclassificados como: linfoma anaplásico de grandes células T (ALTCL – 9/21; 23,9%), linfoma de células T periféricas inespecífico (PTCL-NOS – 4/21; 10,5%), linfoma de células T semelhante à paniculite subcutânea (SPTCL – 4/21; 10,5%), linfoma difuso de grandes células B – variante imunoblástica (DLBCL – 2/21; 5,2%), granulomatose linfomatoide (LYG – 1/21; 2,6%) e linfoma da zona marginal (MZL) do tecido linfoide associado à mucosa (MALT) – variante linfoplasmocítica (1/21; 2,6%). Com base nos achados anatomopatológicos foi possível inferir que diante da suspeita de linfoma cutâneo não epiteliotrópico em cães, ao se deparar com lesões cutâneas múltiplas, nodulares ou placoides e predominantes em tronco e membros, é mais provável que na histopatologia o diagnóstico seja consistente com ALTCL. Por outro lado, perante nódulos ou placas cutâneas solitárias, PTCL-NOS será o tipo histológico mais frequentemente visto. E quando essas lesões estiverem exclusivamente localizadas no tecido subcutâneo, deve-se primeiramente pensar em SPTCL e, mais raramente, em DLBCL. No que se refere aos linfomas cutâneos epiteliotrópicos, a forma cutânea da micose fungoide é a mais comumente observada em cães, em especial, nas fases pré-micótica e micótica. Espera-se essas informações possam auxiliar médicos veterinários clínicos e patologistas em suas rotinas diagnósticas, bem como, contribuir para a caracterização dos linfomas cutâneos não epiteliotrópicos na espécie canina.

TERMOS DE INDEXAÇÃO: Linfomas de pele, tumores cutâneos, linfomas incomuns, dermatopatologia, cães.

INTRODUCTION

Lymphoma is one of the most commonly seen neoplasms in dogs; however, the primarily cutaneous presentation is considered uncommon, making up only 0.2% of all skin tumors and 2% of mesenchymal integumentary neoplasms diagnosed in dogs in Brazil and the United States (Goldschmidt & Shofer 1992, Souza et al. 2006). Based on the human medical literature, canine cutaneous lymphoma is subdivided into epitheliotropic and non-epitheliotropic (Gross et al. 2005, Miller et al. 2013, Mauldin & Peters-Kennedy 2016, Hendrick 2017). Epitheliotropic cutaneous lymphoma harbors tropism for the epidermis and/or adnexal epithelium, originates exclusively from T lymphocytes and comprises three distinct clinicopathological presentations including mycosis fungoides, Sézary syndrome, and pagetoid reticulosis (Gross et al. 2005, Miller et al. 2013, Valli et al. 2016). Non-epitheliotropic cutaneous lymphoma can arise from T lymphocytes, B lymphocytes or null cells (*natural killer* – NK cells), however epitheliotropism is absent and the dermis and/or subcutaneous tissue is involved (Gross et al. 2005, Miller et al. 2013, Valli et al. 2016). The clinical presentation of this form of cutaneous lymphoma is quite diverse and ranges from small papules to large ulcerated masses, which microscopically correspond to a wide variety of histological subtypes, with anaplastic large T-cell lymphoma, nonspecific peripheral T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma being the most commonly described cases on the skin of dogs (Gross et al. 2005, Miller et al. 2013, Valli et al. 2017).

Based on veterinary literature, it is noted that the clinicopathological presentations of epitheliotropic cutaneous lymphoma are already well established for dogs, especially regarding the morphology and distribution pattern of the neoplastic population, with a certain correlation between histopathology and the macroscopic appearance of the lesions (Gross et al. 2005, Fontaine et al. 2010, Miller et al. 2013, Valli et al. 2017). However, although non-epitheliotropic cutaneous lymphoma is also recognized, the clinicopathological correlation is less characterized, as it represents a heterogeneous group of clinical presentations, equally diverse on histopathology, but not yet correlated and that can mimic different skin tumors (Gross et al. 2005, Miller et al. 2013, Moore et al. 2013, Valli

et al. 2016). Therefore, this form of cancer can sometimes configure a diagnostic challenge to the veterinary pathologist. In view of this, the main objective of this article was to establish a possible correlation between the macroscopic presentation and the histological and immunophenotypic subtypes of cutaneous non-epitheliotropic lymphoma in the population of dogs involved in this study. Additionally, we aimed to determine the prevalence of each histological type and subtype of cutaneous lymphoma in canines while also describing the epidemiology and anatomopathology of the cases presented in this study. We hope that our findings regarding these conditions in dogs will assist clinical veterinarians and pathologists in their diagnostic routines.

MATERIALS AND METHODS

Initially, in the Archives of Reports of the "Laboratório de Patologia Veterinária" of the "Universidade Federal de Santa Maria" (LPV-UFSM), the reports of canine cutaneous lymphoma diagnosed from 2000 to 2020 were inspected. Among those necropsy cases and biopsy specimens were considered. Subsequently, the respective paraffin blocks were located in the LPV-UFSM Blocks Archive. Due to the low prevalence of cutaneous lymphoma in dogs, when compared to other forms of lymphoma, in order to substantially increase the number of samples, we contacted different anatomopathological diagnostic laboratories in Brazil and autonomous professionals working in the area, inviting them to participate in our study, collaborating with their respective cases. Our collaborators are also co-authors of this work and include: "Axys Análises – Diagnóstico Veterinário e Consultoria Ltda." (Porto Alegre/RS), "Laboratório de Patologia Animal" (LPA) of the "Universidade Federal de Campina Grande" (UFCG) (Patos/PB), "Laboratório de Histopatologia Veterinária" (LHV) of the "Universidade Estadual Paulista 'Júlio de Mesquita Filho'" (Unesp) (Jaboticabal/SP), "Célula – Laboratório Veterinário" (Eunápolis/BA), and two independent veterinarians working in the area, residing in Rio de Janeiro (RJ) and Belo Horizonte (MG). Individual analysis of the reports of all cases included in the study was performed, and epidemiological, macroscopic, and histopathological information was collected. All cases were histologically reassessed by making slides from paraffin-embedded tissue sections and stained with hematoxylin and eosin (HE). When possible, they were also macroscopically reviewed using photos from the LPV-UFSM Image Archive and collaborating professionals.

The definitive diagnosis of canine cutaneous lymphoma cases was performed based on the histological criteria of the World Health Organization (WHO) for the classification of hematopoietic tumors in humans (Swerdlow et al. 2017), and for the classification of hematopoietic tumors in domestic animals published by the Armed Forces Institute of Pathology (AFIP) (Valli et al. 2002), including its most recent updates for animals (Valli et al. 2016, 2017) and humans (Willemze et al. 2013). In order to confirm the origin of the neoplastic cells and for diagnostic and classification purposes, at least one tissue sample from each case under study was made subject to the immunohistochemistry (IHC) technique, performed in partnership with the "Laboratório de Patologia Morfológica e Molecular" (LAPMOL) of the "Faculdade de Medicina Veterinária e Zootecnia" (FMVZ), of the "Universidade de São Paulo" (USP). Anti-CD20 (RB9013-P, Thermo Fisher Scientific, produced in rabbits) or anti-Pax5 (Clone 24, Biocare Medical, produced in mice) primary antibodies were used for B lymphocytes and anti-CD3 (Clone F7.2.38, Dako Cytomatic, produced in mice) for T lymphocytes, according to the protocols described in Table 1. Lymph nodes from dogs were used as positive controls. The negative control was obtained by omitting the primary antibody and using only the antibody diluent. In addition, to aid in the subclassification of some of the lymphomas, when necessary, IHC was performed for CD56 (CD564 clone, Leica-Novocastra, produced in a mouse). Two of the cases of epitheliotropic cutaneous lymphoma included in this study were previously published by Fighera et al. (2003) and Mazaro et al. (2019) as case reports.

RESULTS

In this study, 54 cases previously diagnosed as canine cutaneous lymphomas by different veterinary pathologists in Brazil were pooled. After histopathological and immunohistochemical reevaluation, 38 cases were confirmed as cutaneous lymphomas. Of these, seven (18.4%) corresponded to necropsies and 31 (81.6%) to biopsy specimens. Of the 38 cases included in this study, 17 (44.7%) were classified as epitheliotropic cutaneous lymphomas (Table 2) and 21 (55.3%) as non-epitheliotropic cutaneous lymphomas (Table 3). Of the epitheliotropic cutaneous lymphomas cases, 13 (34.2%) were subclassified as mycosis fungoides and four (10.5%) as pagetoid reticulosis. Of the 21 cases of non-epitheliotropic cutaneous lymphomas, nine (23.9%) were subclassified as anaplastic large T-cell lymphoma, four (10.5%) as nonspecific peripheral T-cell lymphoma, four (10.5%) as subcutaneous panniculitis-like T-cell lymphoma, two (5.2%) as diffuse large

Table 1. Immunohistochemistry protocols applied for the confirmation of cases of cutaneous lymphomas in dogs

Primary antibody	Antigenic recovery*	Dilution	Incubation (time/temperature)	Secondary antibody[a] and polymer[b] (time/temperature)	Substrate-chromogen
Anti-CD3[c]	Tris-EDTA (pH 9.0)	1:200	30 min/37°C and 18 h/4°C (overnight)	30 min/ambient temperature	DAB[d] **
Anti-CD20[e]	Tris-EDTA (pH 9.0)	1:800	30 min/37°C and 18 h/4°C (overnight)	30 min/ambient temperature	DAB**
Anti-Pax5[f]	Tris-EDTA (pH 9.0)	1:200	30 min/37°C and 18 h/4°C (overnight)	30 min/ambient temperature	DAB**
Anti-CD56[g]	Tris-EDTA (pH 9.0)	1:2000	30 min/37°C and 18 h/4°C (overnight)	30 min/ambient temperature	DAB**

* Performed in a pressure cooker for 20 min with consecutive blocking of endogenous peroxidase and nonspecific reactions at room temperature with hydrogen peroxide (10 volumes) for 30 min and with *Protein Block* (Novolink Kit™) for 10 min, respectively, ** developing time: 3-5 min and counterstaining with Harris hematoxylin; [a] Novolink™ *post primary,* [b] Novolink™ *polymer,* [c] Clone F7.2.38, Dako Cytomatic, produced in mice, [d] DAB = liquid DAB (3,3′ diaminobenzidine) + Substrate chromogen System (Dako), [e] RB9013-P, Thermo Fisher Scientific, produced in rabbits, [f] Clone 24, Biocare Medical, produced in mice, [g] Clone CD564, Leica–Novocastra, produced in mice.

B-cell lymphoma – immunoblastic variant, one (2.6%) as lymphomatoid granulomatosis, and one (2.6%) as marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) – lymphoplasmacytic variant. The epidemiological, anatomopathological, and immunohistochemical findings of the cases will be described below.

Epidemiological findings

Epitheliotropic cutaneous lymphomas. Out of the 17 cases of canine epitheliotropic cutaneous lymphomas, epidemiological information was obtained in 16 of them. Of these, seven (43.8%) were male and nine (56.2%) were female. The age of the affected dogs ranged from six to 15 years, with a mean of 10.3 and a median of 10 years. Purebred dogs (14/16, 87.5%) were predominant and only two were not breed defined (SRD). Purebred breeds included: French Bulldog (4/14), Cocker Spaniel (3/14), Shih Tzu (2/14), Siberian Husky (1/14), Boxer (1/14), Dachshund (1/14), Afghan Hound (1/14), and Golden Retriever (1/14) (Table 2).

Non-epitheliotropic cutaneous lymphomas. Epidemiological data were obtained in 18 of 21 cases of non-epitheliotropic cutaneous lymphomas. The dogs were male and female in 12

Table 2. Epidemiological and pathological findings from cases of cutaneous epitheliotropic lymphoma in dogs

Case	Race	Gender	Age (years)	Macroscopy	Sub classification	IHC*
Canine 1	Siberian Husky	Female	8	Two skin masses, partially ulcerated, in the right pelvic limb (at the level of the knee joint) and in the inguinal region**	Mycosis fungoides (tumor *d'emblée*)	CD3+Pax5-
Canine 2	SRD[a]	Male	10	Skin plaque, partially ulcerated on the pelvic limb (at tibiotarsal joint level)	Mycosis fungoides (tumor *d'emblée*)	CD3+Pax5-
Canine 3	Boxer	Male	10	Nasolabial cutaneous nodule, partially ulcerated	Localized pagetoid reticulosis (*Woringer-Kolopp* disease)	CD3+CD79-
Canine 4	Cocker Spaniel	Female	10	Skin plate in the ventral abdominal region	Mycosis fungoides (tumor *d'emblée*)	CD3+Pax5-
Canine 5	Dachshund	Male	14	Multifocal hypotrichosis and alopecia, progressing to generalized erythematous and exfoliative dermatosis, including some multifocal cutaneous nodules or plaques	Mycosis fungoides (cutaneous form (plaque/mycotic phase))	CD3+Pax5-
Canine 6	NI[b]	NI	NI	Multifocal erythematous dermatosis in the form of arciform lesions	Mycosis fungoides (cutaneous form – erythrodermic/pre-mycotic phase)	CD3+Pax5-
Canine 7	Cocker Spaniel	Female	10	Generalized erythematous and exfoliative dermatosis, with hypotrichosis	Mycosis fungoides (cutaneous form – erythrodermic/pre-mycotic phase)	CD3+Pax5-
Canine 8	French Bulldog	Female	14	Partially ulcerated cutaneous labial nodule	Pagetoid reticulosis (*Woringer-Kolopp* disease)	CD3+Pax5-
Canine 9	Afghan Hound	Male	10	Generalized erythematous and desquamative dermatosis, with hypotrichosis	Pagetoid reticulosis (*Ketron-Goodman* disease)	CD3+Pax5-
Canine 10	French Bulldog	Female	11	Generalized erythematous dermatosis, with alopecia and hypotrichosis, including some multifocal skin nodules or plaques	Mycosis fungoides (cutaneous form (plaque/mycotic phase))	CD3+Pax5-
Canine 11	Golden Retriever	Male	15	Lip skin nodule	Pagetoid reticulosis (*Woringer-Kolopp* disease)	CD3+Pax5-
Canine 12	French Bulldog	Male	8	Depigmentation and ulceration at mucocutaneous junction (lip) and ulcerative lesion on the dorsal surface of tongue	Mycosis fungoides (mucocutaneous and ulcerative forms of the oral mucosa)	CD3+Pax5-
Canine 13	French Bulldog	Male	11	Generalized erythematous dermatosis with hypotrichosis, including multifocal, erythematous, ulcerated plaques, nodules, and skin masses	Mycosis fungoides (cutaneous form – tumour phase)	CD3+Pax5-
Canine 14	Cocker Spaniel	Female	7	Depigmentation and ulceration of mucocutaneous junctions (labial, nasolabial, palpebral, and anal)	Mycosis fungoides (mucocutaneous form)	CD3+Pax5-
Canine 15	Shih-Tzu	Female	12	Generalized erythematous dermatosis, in the form of macules, papules, nodules, and cutaneous plaques, desquamative and partially ulcerated, with alopecia and hypotrichosis	Mycosis fungoides (cutaneous form – plaque/mycotic phase)	CD3+Pax5-
Canine 16	Shih-Tzu	Female	6	Multifocal erythematous dermatosis in the form of arciform lesions on the ventral abdomen, inguinal region and medial aspect of the pelvic limbs	Mycosis fungoides (cutaneous form – erythrodermic/pre-mycotic phase)	CD3+Pax5-
Canine 17	SRD	Female	8	Generalized desquamative and variably erythematous dermatosis, with alopecia and hypotrichosis	Mycosis fungoides (cutaneous form – erythrodermic/pre-mycotic phase)	CD3+Pax5-

* IHC = immunohistochemistry, ** necropsied dog: Canine 1 = metastasis to the lymph nodes (superficial inguinal and internal iliac); [a] SRD = no defined breed, [b] NI = not informed.

(66.7%) and six (33.4%) cases, respectively. The age of the affected dogs ranged from two to 16 years, with a mean of 8.2 and a median of 8.5 years. In 13 (72.2%) of the 18 cases, the dogs were purebred and in five (27.8%) they were of undefined breed (SRD). The pure breeds included: German Shepherd (2/13), Dachshund (2/13), Cocker Spaniel (2/13), Pit Bull (2/13), Fila Brasileiro (1/13), Rottweiler (1/13), Chow-Chow (1/13), Beagle (1/13), and Pug (1/13) (Table 3).

Table 3. Epidemiological and pathological findings from cases of cutaneous non-epitheliotropic lymphoma in dogs

Case	Race	Gender	Age (years)	Macroscopy	Sub classification	IHC*
Canine 1	Fila Brasileiro	Male	2	Multiple homogeneously red or pink, partly ulcerated, hemispherical cutaneous nodules, plaques or masses distributed multifocally over the body, with a homogeneously white cut surface**	Anaplastic large T-cell lymphoma	CD3+Pax5-
Canine 2	Rottweiler	Male	2	Two ulcerated and bleeding skin masses in the distal extremity (carpal region) of the right thoracic limb, with a homogeneously white cut surface**	Peripheral T-cell non-specific lymphoma	CD3+Pax5-
Canine 3	German Shepherd	Male	16	Ulcerated skin mass, in right prescapular region**	Anaplastic large T-cell lymphoma	CD3+Pax5-
Canine 4	Dachshund	Male	8	Ulcerated skin plaque, on the left thoracic limb (at elbow level), with a white and brown mottled cut surface	Mucosa-associated lymphoid tissue marginal zone lymphoma (MALT)	CD3-Pax5+
Canine 5	Cocker Spaniel	Female	7	Diffusely red interdigital cutaneous nodule, located on the left thoracic limb and with a white cut surface	Lymphomatoid granulomatosis	CD3+[a]Pax5+[b]
Canine 6	SRD[c]	Female	2	Cutaneous plaque, with a white cut surface	Anaplastic large T-cell lymphoma	CD3+Pax5-
Canine 7	SRD	Male	10	Alopecic, multifocal cutaneous plaques with a white cut surface	Anaplastic large T-cell lymphoma	CD3+Pax5-
Canine 8	Pit Bull	Male	9	Subcutaneous nodule in the right thoracic region, with a white cut surface	Subcutaneous panniculitis-like T-cell lymphoma	CD3+Pax5-
Canine 9	Cocker Spaniel	Male	10	Partially ulcerated cutaneous labial nodule	Peripheral T-cell lymphoma non-specific	CD3+Pax5-
Canine 10	Chow-Chow	Male	10	Partially ulcerated cutaneous plaque, in the pelvic limb	Peripheral T-cell lymphoma non-specific	CD3+Pax5-
Canine 11	Beagle	Male	11	Partially ulcerated cutaneous plaque, on the thorax	Peripheral T-cell lymphoma non-specific	CD3+Pax5-
Canine 12	SRD	Male	14	Multifocal cutaneous nodules	Anaplastic large T-cell lymphoma	CD3+Pax5-
Canine 13	Pit Bull	Female	5	Cervical subcutaneous plaques and diffuse thickening of subcutaneous tissue, along the ventral region of the trunk, including some nodules on the right lateral aspect of the chest**	Diffuse large B-cell lymphoma - immunoblastic variant	CD3-Pax5+
Canine 14	NI[d]	NI	NI	Multifocal cutaneous nodules	Anaplastic large T-cell lymphoma (epithelioid-like pattern)	CD3+Pax5-
Canine 15	NI	NI	NI	Partially ulcerated cutaneous nodule	Anaplastic large T-cell lymphoma	CD3+Pax5-
Canine 16	NI	NI	NI	Multifocal subcutaneous nodules on the trunk, with a homogeneously white cut surface	Subcutaneous panniculitis-like T-cell lymphoma	CD3+Pax5-
Canine 17	SRD	Male	6	Subcutaneous mass with draining tracts (serosanguinolent fluid), in the right prescapular region, with cervical, thoracic and forearm cranial extensions	Subcutaneous panniculitis-like T-cell lymphoma	CD3+Pax5-
Canine 18	Pug	Female	10	Yellowish-white subcutaneous papules and nodules on the eyelids, vulva, and tail, on the cut surface, evolving with the appearance of multifocal plaques on the dorsal region of the trunk	Subcutaneous panniculitis-like T-cell lymphoma	CD3+CD20-
Canine 19	SRD	Female	7	Ulcerated cutaneous nodules and plaques on thorax, ventral abdomen, inguinal region and medial aspect of the left pelvic limb, with a homogeneously white cut surface**	Anaplastic large T-cell lymphoma	CD3+Pax5-
Canine 20	German Shepherd	Female	12	Multifocal subcutaneous nodules and plaques, on the neck and trunk, with a homogeneously red cut surface**	Diffuse large B-cell lymphoma – immunoblastic variant	CD3-CD20+
Canine 21	Dachshund	Male	7	Homogeneously red, alopecic nodules and cutaneous plaques on the cervical and ventral abdominal regions, inguinal region and medial aspect of the right pelvic limb, with a white cut surface	Anaplastic large T-cell lymphoma (epithelioid-like pattern)	CD3+CD20-

* IHC = immunohistochemistry, ** necropsied dog: Canine 1 = metastases in the lymph nodes (cervical, superficial inguinal, and popliteal), heart, esophagus, stomach, and intestines, Canine 2 = metastases in the lymph nodes (axillary and right prescapular), spleen, lungs, diaphragm, small intestine (jejunum), and heart, Canine 3 = metastasis in the heart and lymph node (right axillary), Canine 13 = metastasis in the right prescapular lymph node and heart, Canine 19 = metastasis in the lymph node (axillary), heart, tongue, tonsil, and oesophagus, Canine 20 = metastasis in the left superficial inguinal lymph node; [a] CD3 = random immunolabeling of reactive lymphocytes, [b] Pax5 = random immunolabeling of neoplastic lymphocytes, [c] SRD = no defined breed, [d] NI = not informed.

Anatomopathological and immunophenotypic findings

Mycosis fungoides. Out of the 13 cases of mycosis fungoides, eight (21.1%) corresponded to the classic form of disease presentation (cutaneous form), three (7.9%) to the tumor *d'emblée*, one (2.6%) to the mucocutaneous form, and one (2.6%) to the mucocutaneous and ulcerative forms of the oral mucosa occurring concomitantly. Of the eight cases diagnosed as the cutaneous form of mycosis fungoides, four presented clinically in the premycotic phase, also recognized as erythrodermic or spotting. These cases were characterized by multifocal erythematous dermatosis in the form of arciform lesions (2/4) (Fig.1), or by a variably erythrodermic and generalized exfoliative presentation (2/4), accompanied by alopecia and/or hypotrichosis (Fig.2). In three other cases (3/8), lesions were seen in a more advanced stage, where besides a generalized erythematous dermatosis (3/3), exfoliative (2/3) or not (1/3), with hypotrichosis and alopecia (3/3), papules, nodules and/or plaques, desquamative and/or ulcerated (3/3) were formed, evidencing the phase of the disease known as mycotic or plaque phase (Fig.3). In the remaining case (1/8), the lesions evolved to the tumor phase, with the presence of cutaneous, ulcerated, and exudative masses (Fig.4), multifocally distributed over the body surface, but mainly on the head and limbs.

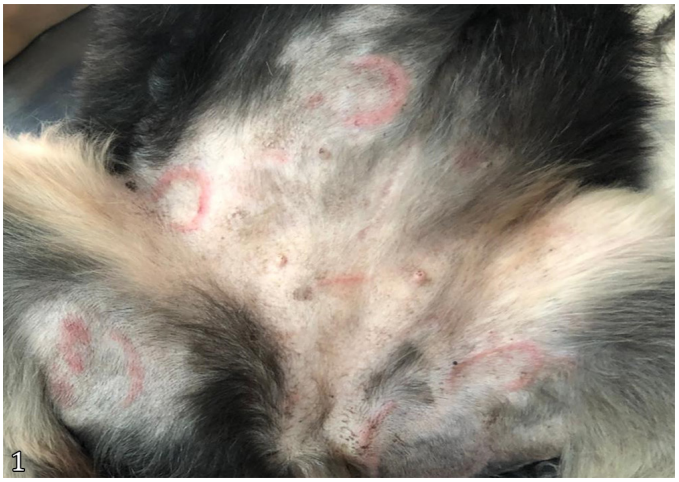

Fig.1. Mycosis fungoides, cutaneous form (premicotic or spotting phase), skin, dog. Multifocal erythematous dermatosis, in the form of arciform lesions, on the ventral abdomen, inguinal region, and medial face of the pelvic limbs.

Fig.2. Mycosis fungoides, cutaneous form (premicotic or spotting phase), on dog skin. Generalized desquamative and variably erythematous dermatosis, with severe alopecia and hypotrichosis.

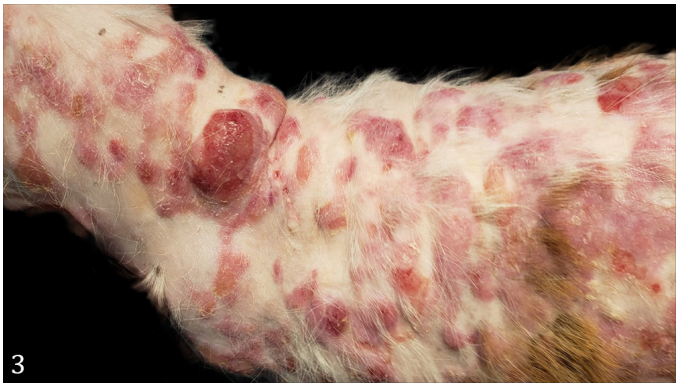

Fig.3. Mycosis fungoides, cutaneous form (mycotic or plaque phase) on dog skin. In addition to a generalized erythrodermic presentation, with alopecia and hypotrichosis, several plaques can be observed, equally erythematous, desquamative and ulcerated, multifocally distributed throughout the body.

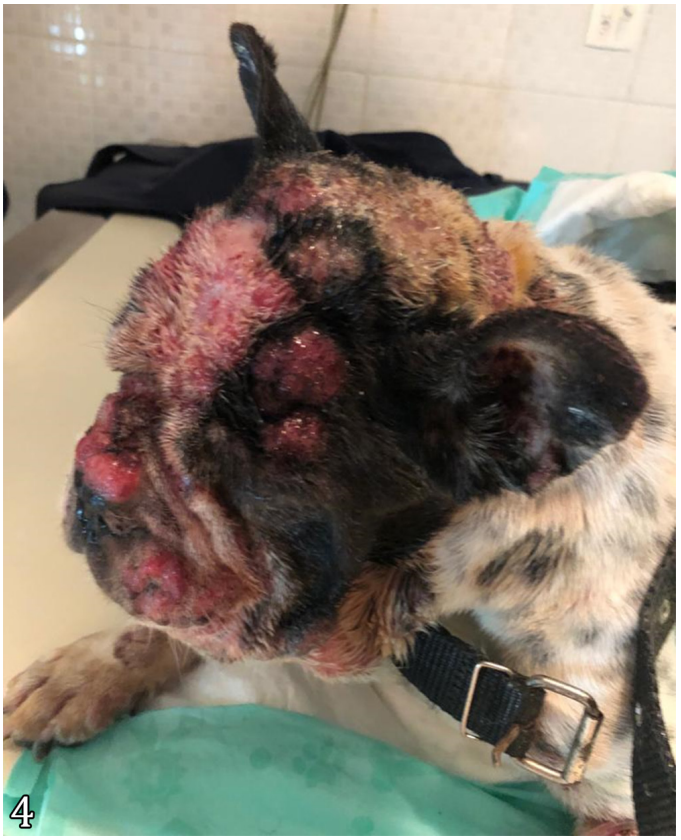

Fig.4. Mycosis fungoides, cutaneous form (tumor phase) on dog skin. Presence of multifocal, erythematous, ulcerated and exudative masses on the face.

In two of the three cases diagnosed as tumor *d'emblée*, the lesions consisted of solitary plaques, ulcerated (1/2) or not (1/2), located in the pelvic limb or ventral abdominal region. In the remaining case (1/3), the condition was characterized by the presence of two cutaneous masses, partially ulcerated and located in the caudal region of the body, especially in the right pelvic limb and inguinal region. Additionally, this dog was necropsied and regional nodal metastasis (superficial inguinal and internal iliac lymph nodes) was identified. In the case in which the mucocutaneous form was observed there was depigmentation and ulceration of the nasolabial (Fig.5), labial, palpebral, and anal mucocutaneous junctions. And in the remaining case, the mucocutaneous and ulcerative forms of the oral mucosa were seen concomitantly, as an ulcerative lesion on the dorsal surface of the tongue together with depigmentation and ulceration of the labial mucocutaneous junction.

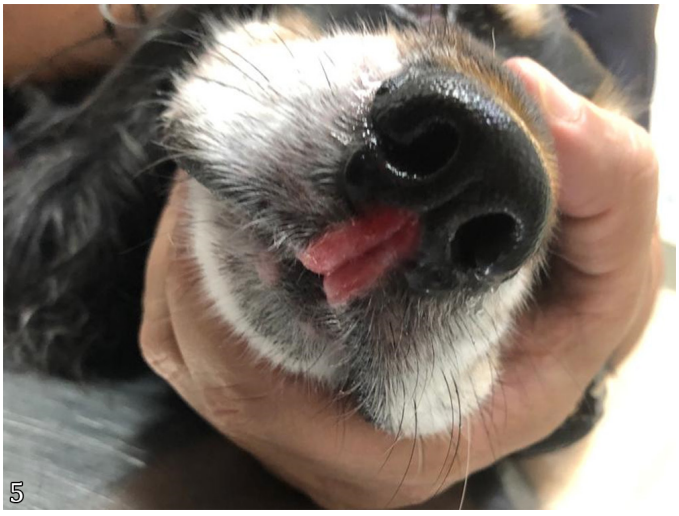

Fig.5. Mycosis fungoides, mucocutaneous form on dog skin. There is depigmentation and ulceration of the nasolabial region.

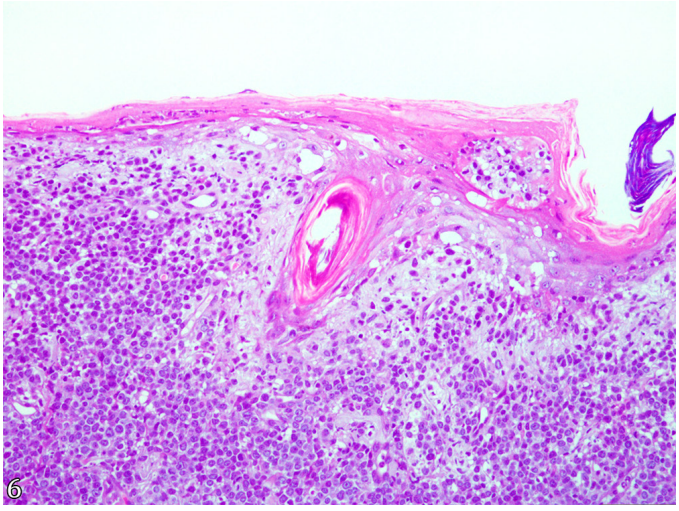

Fig.6. Mycosis fungoides on dog skin. Note that the neoplastic lymphocytes diffusely obliterate the superficial dermis and invade the epidermis as an aggregate, which characterizes a Darier-Pautrier microabscess, a classic finding of this type of lymphoma. HE, obj.20x.

Regardless of the macroscopic presentation, all cases of mycosis fungoides were histologically characterized by a densely cellular, poorly demarcated, nonencapsulated neoplastic lymphoid proliferation, located mainly in the superficial dermis, which extended into the deep dermis, with rare expansion into the subcutaneous tissue. Neoplastic lymphocytes, in their majority, compressed and diffusely invaded the epidermis or formed aggregates of various dimensions, called Darier-Pautrier microabscesses (Fig.6). The adnexal epithelium was frequently infiltrated and variably replaced by neoplastic cells, sometimes including invasion of the sebaceous and sweat glands. Neoplastic lymphocytes were round or oval, of intermediate volumes (nuclear diameter >1.5 erythrocyte and <2 erythrocytes), with small to moderate amounts of homogeneous, eosinophilic cytoplasm. The nuclei were round, oval, endentate, reniform, and sometimes irregular (cerebriform pattern). When irregular, these nuclei characterized neoplastic lymphocytes designated as "mycosis cells". Single, small, basophilic nucleoli were variably observed. The mean mitotic count of the cases was 12 figures in 2.37mm^2. Moreover, moderate nuclear pleomorphism was observed. Skin ulceration arising especially from epidermal invasion, but also from neoplastic compression, was commonly noted. On IHC, in all cases, neoplastic lymphocytes showed diffuse cytoplasmic marking for CD3 (Fig.7) and negativity for Pax5 or CD20, demonstrating their T lymphocyte origin.

Pagetoid reticulosis. The localized form of the condition (Woringer-Kolopp disease) was observed in three (7.9%) of the four cases diagnosed as reticulosis pagetoid, while the disseminated form (Ketron-Goodman disease) was only observed in one case (2.6%). The localized presentation of the disease was seen as solitary nodules, partially ulcerated (2/3) or not (1/3), located on the head, especially in the labial (2/3) or nasolabial (1/3) regions. In the disseminated form there was generalized erythematous and desquamative dermatosis, with hypotrichosis, similar to the erythrodermic cutaneous form of mycosis fungoides. Histologically, both in its localized and disseminated form, pagetoid reticulosis was characterized by a densely cellular, well-demarcated, non-encapsulated, infiltrative

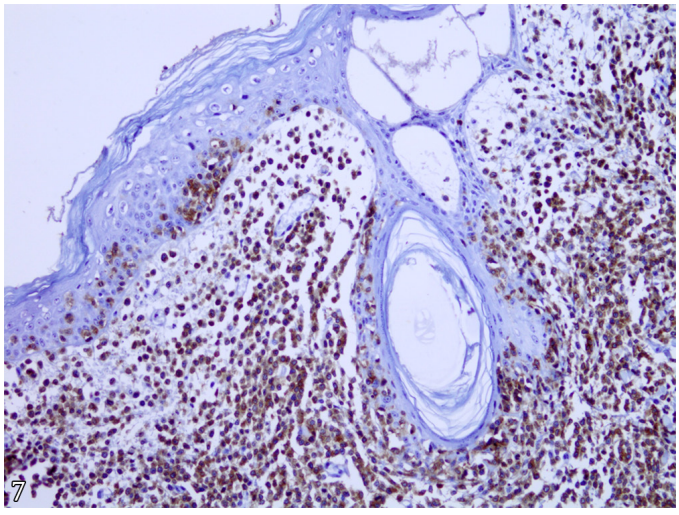

Fig.7. Mycosis fungoides on dog skin. Neoplastic lymphocytes intensely immunolabeled for CD3, evidencing their T origin. Invasion of the epidermis and adnexal epithelium can be easily noted. IHC, obj.20x.

proliferation, almost entirely restricted to the epidermis and adnexal epithelium (Fig.8). The neoplastic cells were arranged in nests or cords, both separated by the remaining keratinocytes. Such cells were round, large (nuclear diameter ≥2 erythrocytes) and with moderate amount of homogeneous and eosinophilic or clear cytoplasm, which gave them an appearance of "cytoplasmic emptiness". The nuclei were round, oval, or reniform, centrally located and constituted by loose, sometimes vesicular chromatin. Nucleoli were single, small, basophilic, and variably evident. The mean mitotic count of the cases was 5 figures in 2.37mm^2. In two of the four cases, neoplastic lymphocytes could be seen multifocally in the superficial dermis, but in small quantity. On IHC, neoplastic lymphocytes showed intense diffuse cytoplasmic immunostaining for CD3 (Fig. 9) and were negative for Pax5, demonstrating their T lymphocyte origin.

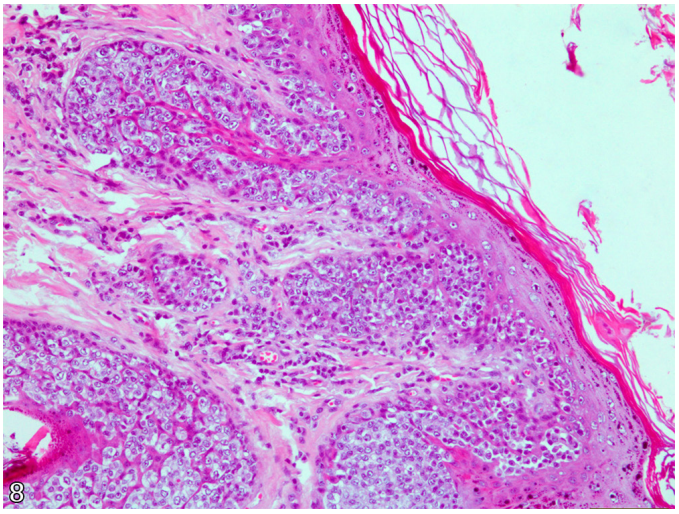

Fig.8. Pagetoid reticulosis, on dog skin. Neoplastic population almost exclusively confined to the epidermis and adnexal epithelium, a characteristic finding of this type of lymphoma. The neoplastic lymphocytes are large, have clear or pale cytoplasm and form nests or cords, separated by the remaining keratinocytes. HE, obj.20x.

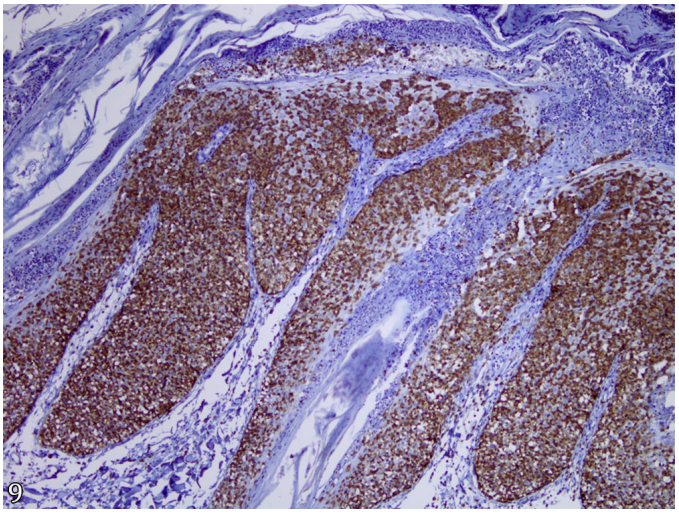

Fig.9. Pagetoid reticulosis, on dog skin. Neoplastic lymphocytes with intense cytoplasmic immunolabeling for CD3, confirming their T cell origin and highlighting the major localization of the neoplastic population. IHC, obj.10x.

Anaplastic large T-cell lymphoma. In six (15.9%) of the nine cases diagnosed as cutaneous anaplastic large T-cell lymphoma, the lesions were multiple and multifocally distributed over the body surface. In three of these cases, the location of the majority of lesions was reported to be exclusively along the ventral region of the body, on the neck, trunk, and pelvic limbs. Macroscopically, most lesions (5/6) consisted of nodules and/or plaques, ulcerated (3/6) or not (3/6), eventually alopecic (2/6) and/or homogeneously red to pink (2/6) (Figs.10 and 11). Some masses were observed concomitant to nodules and plaques, in only one of the cases. In the remaining three cases (8%), the lesions were solitary and were seen in the form of nodules (1/3), plaques (1/3) and masses (1/3), covered by ulcerated skin (2/3) or not (1/3). In six (15.8%) out of nine cases, the lesions were soft to touch and cut and had homogeneously white surface when cut. In the remaining cases, such information was not obtained. Necropsy was performed in three of the nine cases, showing regional nodal metastasis in the form of nodular (2/3) or diffuse (1/3) lymphadenomegaly, and forming nodules, plaques, or focally extensive infiltration in the heart (3/3), esophagus (2/3), tongue (1/3), stomach (1/3), and intestines (1/3).

Histologically, in all cases, the skin lesions were composed of dense proliferation of neoplastic lymphocytes, organized in a mantle, which dissected and replaced a large part of the superficial and deep dermis, sparing the adnexal epithelium and epidermis. However, due to the compressive activity exerted by the neoplastic population, there was epidermal thinning, with or without ulceration. In all cases the neoplastic population extended to the subcutaneous tissue, but rarely invaded the adjacent muscles (2/9). In most cases (7/9, 18.6%), the neoplastic lymphocytes represented the most commonly described pattern (classic pattern) for this histological type of cutaneous lymphoma, i.e., they were predominantly large, round or oval and formed by moderate or abundant amount of homogeneous and eosinophilic or pale cytoplasm. The nuclei were round, oval, endentate or irregular, central and composed of loose, sometimes vesicular

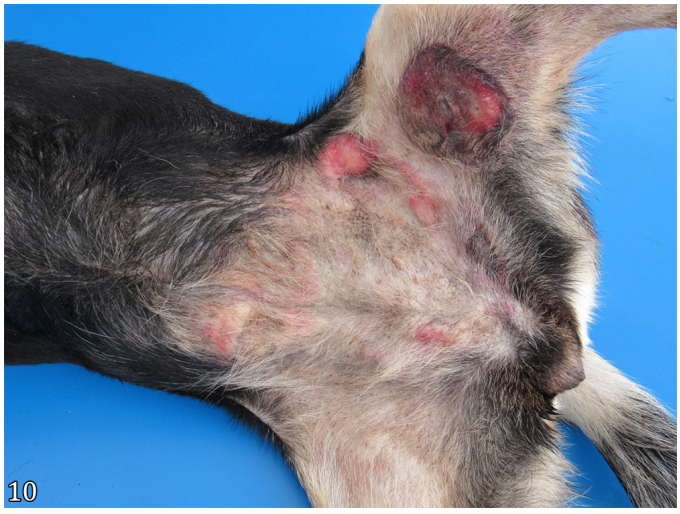

Fig.10. Cutaneous anaplastic large T-cell lymphoma on dog skin (ventral abdomen, inguinal region and medial aspect of left pelvic limb). Presence of nodules and plaques, multifocal and covered by partially or totally ulcerated skin.

chromatin. The nucleoli were single or multiple, variable in size, basophilic and conspicuous (Fig.12). The mean mitotic count of the cases was 50 figures in 2.37mm^2. Additionally, some larger-than-average cells with horseshoe-shaped or reniform nuclei were found, which are called "*hallmark* cells" classically seen in anaplastic lymphomas. Binucleated cells were frequently observed, including some morphologically similar to Reed-Sternberg cells, i.e., they had identical and closely related nuclei arranged as a "mirror image" and large and conspicuous "owl-eyed" nucleoli. Randomly, among the neoplastic lymphocytes, macrophages with cellular debris (tingible or lymphogranular corpuscles) were observed.

In the two remaining cases (2/9, 5.3%), the cell morphology drew attention, especially regarding the degree of atypia. The neoplastic lymphocytes were arranged in mantle, however, the cell boundaries were predominantly indistinct, being perceptible only at the periphery of the lesions. The cells had moderate or abundant amounts of homogeneous and eosinophilic cytoplasm, with large, round or oval, central nuclei formed mostly by vesicular chromatin. The nucleoli were large, amphophilic, conspicuous, and their number ranged from one to three (Fig.13). Mitotic counts corresponded for each case to 34 and 46 figures in 2.37mm^2. The neoplastic population resembled epithelial cells, resembling an undifferentiated carcinoma. Based on human medical literature, this morphological pattern of anaplastic cutaneous lymphoma is recognized as epithelioid-like. Neoplastic lymphocytes that are binucleated or have more than two nuclei (multinucleated) were commonly seen. In some multinucleated cells, the nuclei were peripherally organized, characterizing a "wreath-like" nuclear pattern. Among the neoplastic population there was a large amount of macrophages with lymphogranular corpuscles, which gave the tumor, at lower magnification, a "starry-sky" pattern. Despite the different morphological patterns, on

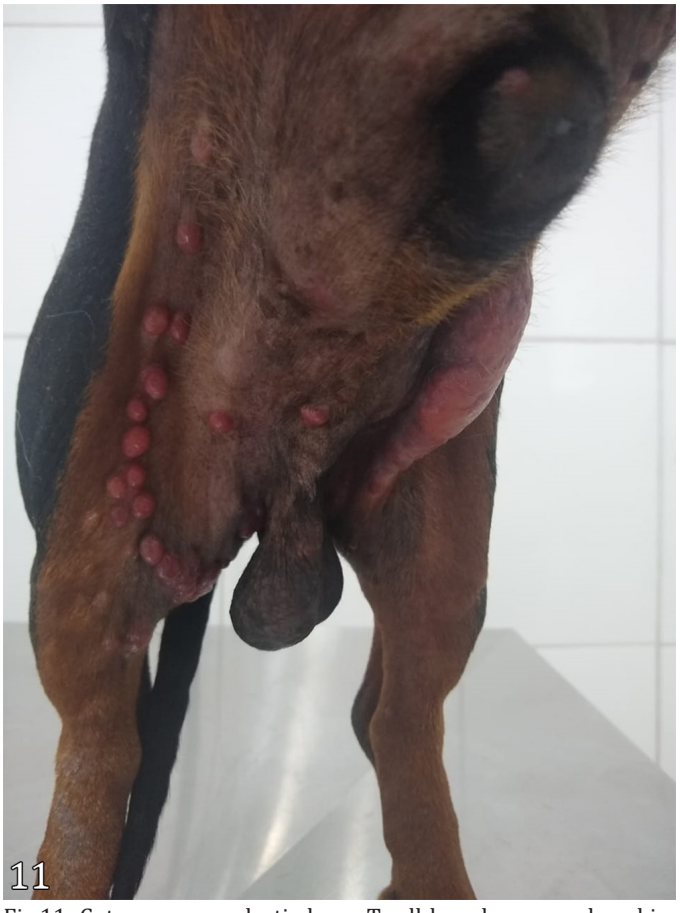

Fig.11. Cutaneous anaplastic large T-cell lymphoma on dog skin. Ventral abdomen, inguinal region, and medial aspect of the right pelvic limb, with several nodules, homogeneously red, including some coalescing into a large plaque.

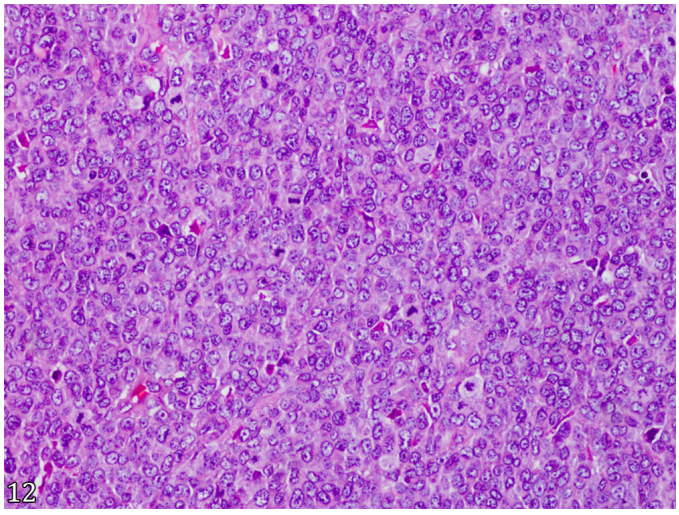

Fig.12. Anaplastic cutaneous large T-cell lymphoma on dog skin. Large neoplastic lymphocytes, organized in mantle. There is marked variation in nuclear morphology. Note that the nuclei are formed by loose chromatin and have single or multiple, basophilic, evident nucleoli. Additionally, various figures of mitosis can be noted. HE, obj.40x.

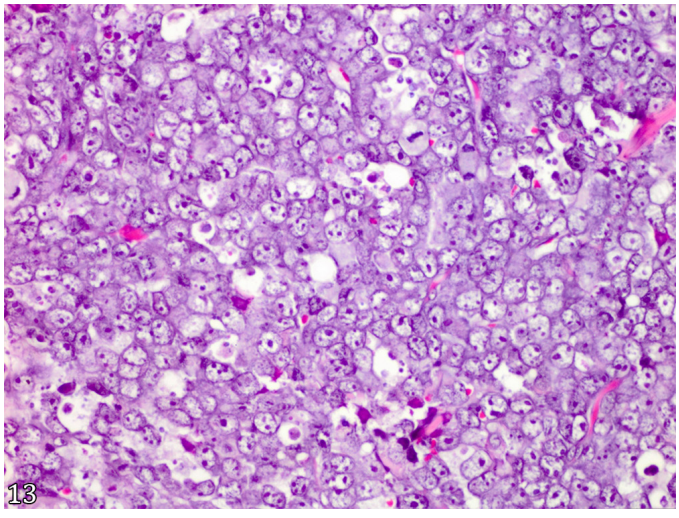

Fig.13. Anaplastic large T-cell lymphoma (epithelioid-like pattern) on dog skin. Sharply atypical neoplastic lymphoid population, resembling an undifferentiated carcinoma. Note that the neoplastic lymphocytes have predominantly indistinct cell boundaries and round or oval nuclei, formed by vesicular chromatin. Nucleoli range from one to three and are large, amphophilic, and conspicuous. Lymphogranular corpuscles are seen in large numbers. HE, obj.40x.

IHC, all cases subclassified as anaplastic cutaneous large cell lymphoma were positive for the T lymphocyte marker (CD3) (Fig.14), presenting diffuse cytoplasmic immunostaining, and negative for the B lymphocyte marker (Pax5).

Nonspecific peripheral T-cell lymphoma. Out of the four cases (4/38, 10.5%) diagnosed as cutaneous peripheral T-cell nonspecific lymphoma, three (7.9%) presented clinically as solitary lesions, seen in the form of nodule (1/3) or plaques (2/3), both covered by partially ulcerated skin and randomly located on the lip (1/3), pelvic limb (1/3), and chest (1/3). In the remaining case (1/4), two large, ulcerated, and bleeding masses were observed, intimately disposed at the distal end of the right thoracic limb, especially at carpal level. This dog was necropsied, so it was noted that the cutaneous masses were soft to the touch and to the cut, and had homogeneously white surfaces when cut. In addition, metastases were found in lymph nodes (axillary and right prescapular), spleen, lungs, diaphragm, small intestine (jejunum), and heart. The lesions observed in the four cases were histologically composed of a dense monomorphic population of neoplastic lymphocytes, organized in a mantle, which dissected and diffusely replaced the superficial and deep dermis, but without invading the epidermis and adnexal epithelium. Discrete fibrovascular stroma was variably noted. The neoplastic lymphocytes had intermediate volumes and were composed of small amount of homogeneous and eosinophilic cytoplasm. The nuclei were predominantly round or oval, central, and formed by loosely arranged chromatin. The nucleoli were single, of intermediate volume, basophilic, and evident (Fig.15). The mean mitotic count of the cases was 14 figures in 2.37mm^2. In all cases, neoplastic lymphocytes showed diffuse cytoplasmic immunolabeling for CD3 (Fig.16) and no immunolabeling for Pax5.

Subcutaneous panniculitis-like T-cell lymphoma. Of the four (4/38, 10.5%) cases diagnosed as subcutaneous panniculitis-like T-cell lymphoma, two (5.2%) showed solitary lesions, and the other two (5.2%) showed multiple lesions. Two distinct macroscopic presentations were seen in the cases presenting with solitary lesions. The first was characterized by a subcutaneous nodule, covered by non-ulcerated skin, and with a white or yellowish-white cut surface, located in the right thoracic region. The second presentation corresponded to a large subcutaneous mass, 16 x 8.5cm in its largest axis, predominantly located in the right prescapular region, but with extension to the neck, chest and cranial portion of the forearms (Fig.17). Additionally, the mass was covered by slightly erythematous skin, with multifocal ulcers and draining tracts, from which serosanguinous fluid flowed. In cases in which the lesions were multiple (2/4, 5.2%), subcutaneous nodules (2/2) were mostly observed (Fig.18), but also some papules (1/2) and plaques (1/2), mostly distributed over the trunk (2/2). These lesions had a homogeneously yellowish-white cut surface (Fig.18 inset).

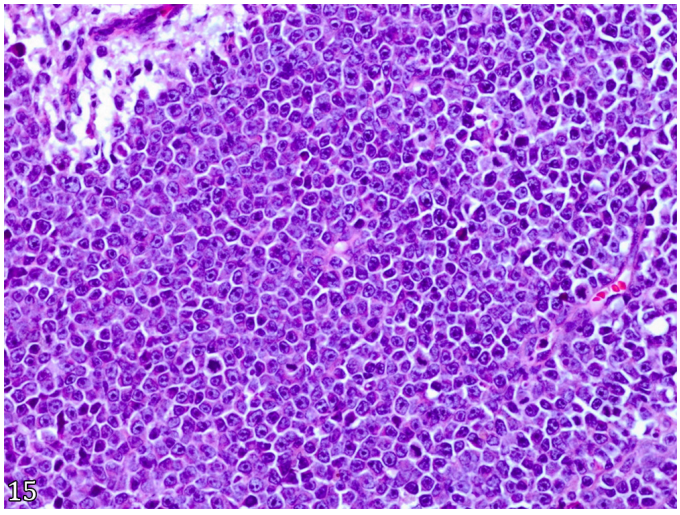

Fig.15. Nonspecific cutaneous peripheral T-cell lymphoma, on dog skin. Monomorphic neoplastic population, without cell atypia, easily allowing the diagnosis of lymphoma. Note that the neoplastic lymphocytes are organized in mantle, are medium size and formed by a small amount of homogeneous and eosinophilic cytoplasm. They have round or oval nuclei, central and formed by loose chromatin. The nucleoli are single, of intermediate volumes, basophilic, and conspicuous. HE, obj.40x.

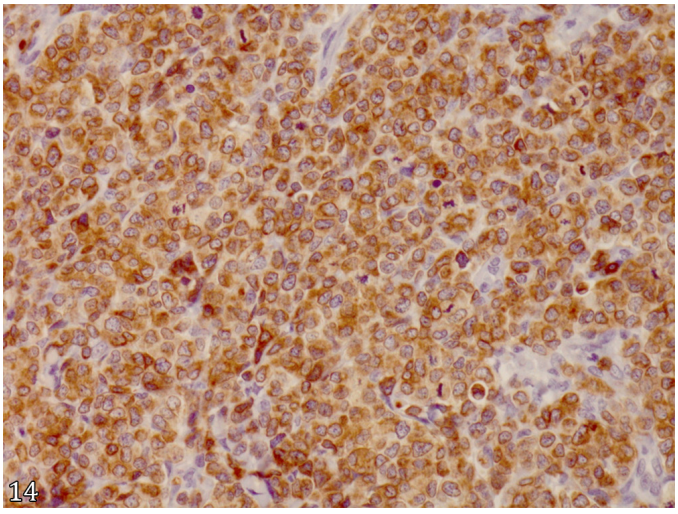

Fig.14. Anaplastic large T-cell lymphoma, on dog skin. Neoplastic lymphocytes with intense cytoplasmic immunostaining for CD3. IHC, obj.40x.

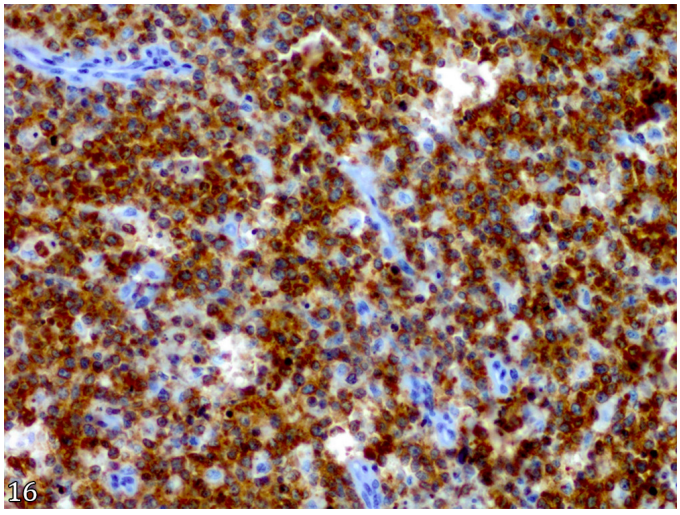

Fig.16. Nonspecific peripheral T-cell lymphoma, on dog skin. Neoplastic lymphocytes intensely immunolabeled for CD3. IHC, obj.40x.

On histopathology, these lesions were characterized by densely cellular lymphoid proliferation, which infiltrated and diffusely replaced the subcutaneous tissue or formed lobules separated by thin collagenous stroma. In sites where the subcutaneous tissue was less intensely affected, the neoplastic lymphocytes surrounded closely related adipocytes, giving the tissue a lace-like pattern. In some lesions, the neoplastic population extended into the dermis, but without invading the adnexal epithelium and/or epidermis. In larger lesions, there was epidermal thinning and/or ulceration due to the compressive activity exerted by the neoplastic population. The neoplastic lymphocytes were small or medium sized and had small or moderate amount of homogeneous and eosinophilic cytoplasm. They had round or oval nuclei, central, and formed by loose chromatin. The mean mitotic count of the cases was 9 figures in 2.37mm^2. Nucleoli were single, small or medium, basophilic, and variably evident (Fig.19). Randomly, macrophages with tingible corpuscles and apoptotic neoplastic lymphocytes were observed, characterized by condensed nuclei in a round, homogeneous, and intensely basophilic mass. On IHC, the neoplastic population showed diffuse cytoplasmic immunolabeling for CD3 and negative for CD20 and CD56, confirming its T lymphocyte origin.

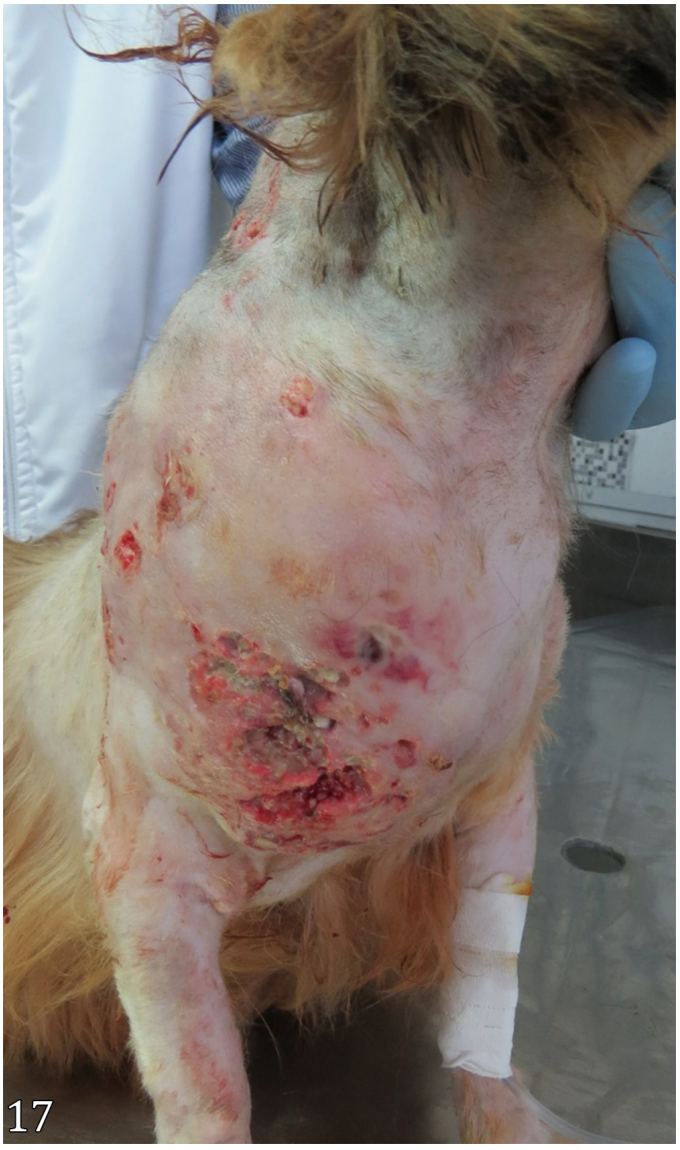

Fig.17. Subcutaneous panniculitis-like T-cell lymphoma, subcutaneous tissue of a dog. Large subcutaneous mass involving the right prescapular, cranial thoracic, and ventral cervical regions, with extension to the cranial aspect of the thoracic limbs. Note that the mass is covered by partially ulcerated and erythematous skin, including tracts draining serosanguinous fluid.

Fig.18. Subcutaneous panniculitis-like T-cell lymphoma, subcutaneous tissue (tail), of a dog. Subcutaneous nodule, covered by ulcerated skin, which makes it homogeneously red, at natural surface. Inset: cut surface of the nodule of the tail. The tumor is yellowish-white and circumferentially involves the coccygeal vertebra.

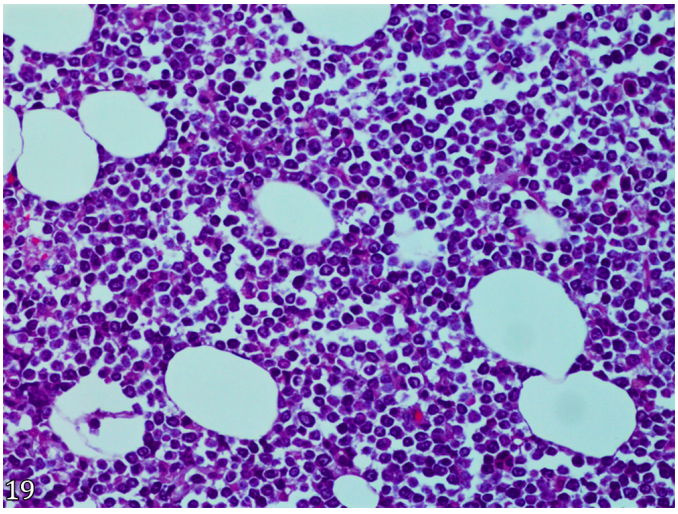

Fig.19. Subcutaneous panniculitis-like T-cell lymphoma, subcutaneous tissue, of a dog. There is diffuse replacement of a significant amount of the subcutaneous tissue by neoplastic lymphocytes, leaving few adipocytes. The lymphocytes are mostly small and have scanty cytoplasm, homogeneous and eosinophilic. The nuclei are mostly round, central, and formed by loosely arranged chromatin. The nucleoli are single, small, basophilic and variably evident. HE, obj.40x.

Diffuse large B-cell lymphoma – immunoblastic variant. In both cases diagnosed as diffuse large B-cell lymphoma – immunoblastic variant (2/38, 5.2%), the lesions originated from the subcutaneous tissue. Macroscopically, in one of these cases (1/2), several multifocal subcutaneous nodules and plaques were observed, mostly located in the neck and dorsal region of the trunk. The skin covering the lesions was variably erythematous, but rarely ulcerated (Fig.20). The lesions were soft to touch and cut and had lobulated and homogeneously red cut surface (Fig.20 inset). Invasion of the skin and adjacent musculature was noted on the cut surface of some plaques. This dog was submitted to necropsy and metastasis was found in the left superficial inguinal lymph node. In the other case (1/2), some subcutaneous nodules and plaques were also observed, located in the ventral cervical region and lateral face of the thorax. However, diffuse subcutaneous tissue involvement was the predominant and most easily observed finding at necropsy. Along the ventral region of the trunk, much of the subcutaneous tissue was replaced by a lobulated and homogeneously red or pink tissue. That tissue was markedly thickened in all its extension. This dog was also necropsied and metastases were observed in the right prescapular lymph node and heart.

On histopathology in both cases, the subcutaneous lesions corresponded to dense neoplastic lymphoid proliferation that infiltrated and replaced the subcutaneous tissue. The neoplastic lymphocytes formed large lobules, which were separated by thin collagenous fibers, and surrounded adipocytes, giving the tissue an aspect similar to the pattern denominated as "lace-like", described for T-cell lymphoma similar to subcutaneous panniculitis. Occasionally, in some lesions, the neoplastic population expanded towards the dermis, dissecting it, but sparing the skin appendages and epidermis. Although there was no invasion of the epidermis, in some sites it was thin due to the compressive activity exerted by the neoplastic population. The neoplastic lymphocytes were large, round or oval and formed by small to moderate amount of homogeneous and eosinophilic cytoplasm. The nuclei were round, oval or endentate, central, and constituted by loose or vesicular chromatin. Nucleoli were mostly single, large, eosinophilic or basophilic, and conspicuous (Fig.21). The mitotic counts of the cases were 34 and 41 figures in 2.37mm^2. There was moderate nuclear pleomorphism and mild anisocytosis. Binucleated cells were randomly observed. Multifocally, among the neoplastic cells, several macrophages with lymphogranular corpuscles were seen, characterizing high phagocytic activity. In both cases, the neoplastic lymphocytes presented intense membrane immunolabeling for CD20 and negativity for CD3, demonstrating their origin in B lymphocytes.

Lymphomatoid granulomatosis. The only case (1/38, 2.6%) diagnosed as lymphomatoid granulomatosis in this study was macroscopically characterized by a soft, diffusely red, cutaneous nodule with a homogeneously white cut surface. The lesion was located in the interdigital region of the left thoracic limb. Histologically there was dense proliferation of round cells arranged as dermal perivascular cuffs in an angiocentric pattern. These proliferated cells formed a mixed population composed of small mature lymphocytes with scanty cytoplasm and round nuclei formed by dense chromatin. The other population was composed of neoplastic lymphocytes of intermediate size and by histiocytes and/or macrophages. The neoplastic lymphocytes had moderate amounts of homogeneous and eosinophilic cytoplasm. They had round or oval nuclei, central, and formed by loose chromatin. Nucleoli were variably noted. The mitotic count was 2 figures in 2.37mm^2. On IHC, neoplastic lymphocytes showed intense nuclear immunolabeling for B lymphocyte marker (Pax5) and negativity for T lymphocyte marker (CD3). The small mature lymphocytes, considered reactive, immunolabeled for CD3 and did not show immunolabeling for Pax5.

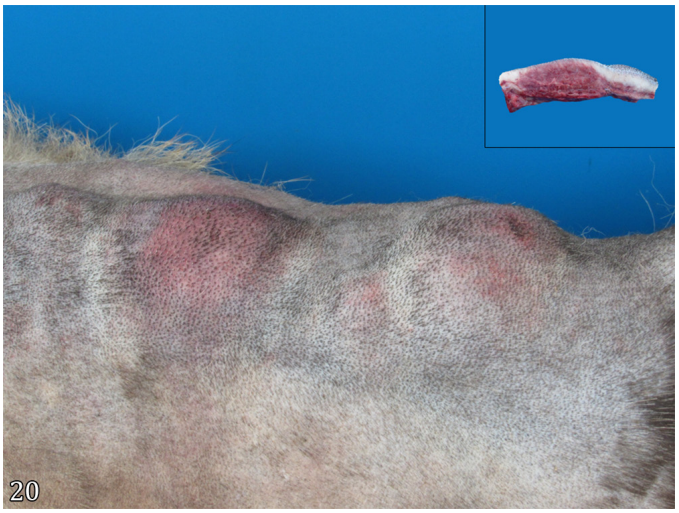

Fig.20. Diffuse large B-cell lymphoma – immunoblastic variant, subcutaneous tissue of the back, of a dog. Presence of subcutaneous nodules, covered by erythematous skin, including discrete ulceration of the nodule on the right (nodular pattern). Inset: homogeneously red cut surface of one of the subcutaneous nodules. Additionally, it can be noted that the infiltration of the subcutaneous tissue forms discretely delimited lobules.

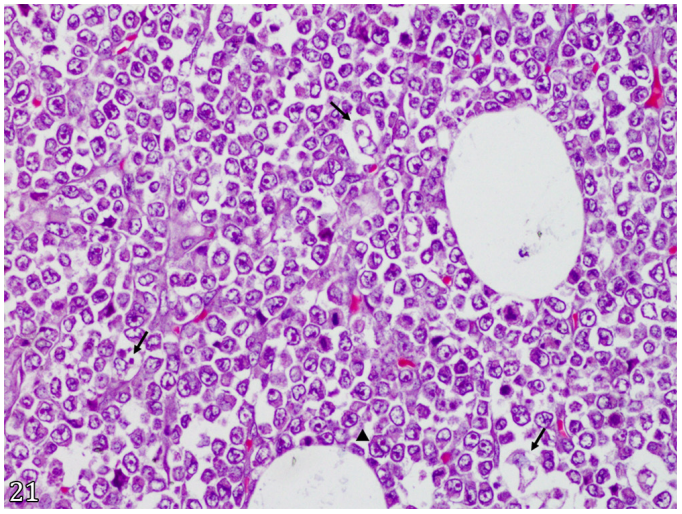

Fig.21. Diffuse large B-cell lymphoma – immunoblastic variant, subcutaneous tissue, of a dog. Dense population of large neoplastic lymphocytes, organized in a mantle, diffusely replacing the subcutaneous tissue. The lymphocytes have central, round, oval or irregular nuclei composed mostly of vesicular chromatin. The nucleoli are single, large, eosinophilic, and conspicuous. Macrophages with lymphogranular corpuscles (arrows) show high phagocytic activity. Binucleated cells are eventually noted (arrowhead). HE, obj.40x.

Marginal zone lymphoma of MALT – lymphoplasmacytic variant. The case diagnosed as marginal zone lymphoma of MALT – lymphoplasmacytic variant (1/38, 2.6%), consisted of an ulcerated plaque that was soft to the touch, located at the level of the elbow, on the left thoracic limb. It was also soft to the cut and had white and brown mottled cut surface. Histologically, this plaque was formed by a dense, monomorphic lymphoid population, giving the tumor a darker appearance as compared with the most commonly seen variant (conventional variant) of the marginal zone lymphoma originating from MALT. The neoplastic population was mantle organized, with infiltration and diffuse replacement of the dermis, but without invading the epidermis and/or the adnexal epithelium. The neoplastic lymphocytes were small or medium-sized and had sparse, homogeneous, eosinophilic cytoplasm. Nuclei were predominantly round, central or eccentric, and formed by more densely arranged chromatin. Single, small, and basophilic nucleoli were variably observed (Fig.22). Mitotic count was 1 figure in 2.37mm^2. The lymphocytes with eccentric nuclei, were interpreted as lymphoplasmocytoid cells, which together with the rare plasma cells seen at the periphery of the lesion, characterize the lymphoplasmocytic variant. No germinal centers were observed among the neoplastic cells, only some remnant or reactive T lymphocytes, which were identified against CD3 positivity on IHC. Neoplastic lymphocytes showed intense nuclear immunostaining for Pax5 and negativity for CD3, evidencing their B lymphocyte origin.

DISCUSSION

According to the literature, epitheliotropic cutaneous lymphomas in dogs are more prevalent when compared to non-epitheliotropic ones (Moore & Olivry 1994, Gross et al. 2005, Hendrick 2017), unlike what was observed in this study, in which the non-epitheliotropic presentation was the most frequent, making up slightly more than half of the cases. With regard to epitheliotropic cutaneous lymphomas, cases of mycosis fungoides, especially in the cutaneous form, in the erythrodermal or plaque phase, were predominant, whereas, cases of pagetoid reticulosis were uncommon, especially in its disseminated form (Ketron-Goodman disease), which was diagnosed in only one dog, corroborating the findings in the literature (Gross et al. 2005, Moore et al. 2009, Fontaine et al. 2010, Miller et al. 2013, Azuma et al. 2021). Additionally, because this was an exclusively anatomopathological study, no cases of Sézary Syndrome were pointed out, since the diagnosis of this condition is made before the presence of neoplastic lymphocytes (Sézary cells) in the peripheral blood, which represents the leukemization of a cutaneous presentation of mycosis fungoides, with regional nodal involvement (Gross et al. 2005, Fontaine et al. 2009, Miller et al. 2013, Valli et al. 2016, Hendrick 2017). Regarding the epidemiological findings of the cases diagnosed as epitheliotropic cutaneous lymphomas, elderly dogs (11/16, 68.7%) and purebred dogs (14/16, 87.5%), were predominantly affected, corroborating what has been described for the species (Moore et al. 2009, Fontaine et al. 2010, Miller et al. 2013), however, predilection by gender was not observed.

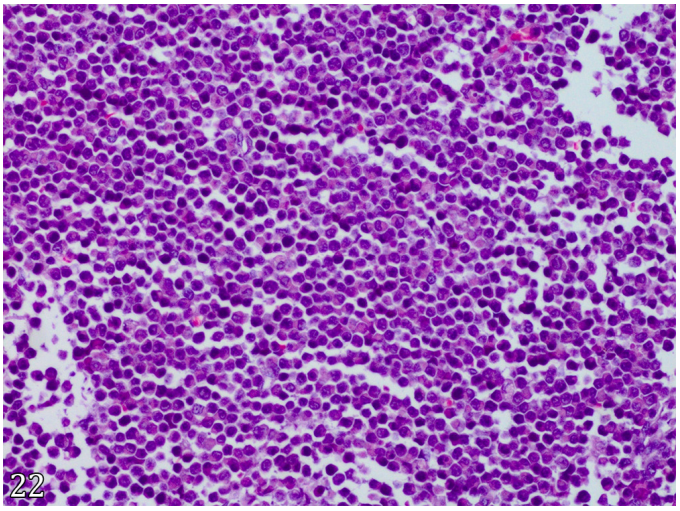

Fig.22. Marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) – lymphoplasmacytic variant, on dog skin. Monomorphic neoplastic lymphoid population, arranged in a mantle and with more densely arranged nuclear chromatin, giving the tumor a darker appearance, different from what is traditionally seen in the conventional variant of this type of lymphoma. The neoplastic lymphocytes are small, with scant cytoplasm, round and central nuclei, resembling small mature lymphocytes or have eccentric nuclei in a plasmacytoid pattern. HE, obj.40x.

Regarding non-epitheliotropic cutaneous lymphomas, the most frequent type in this study, regarding histological subtypes, corroborating what is already described for dogs (Valli et al. 2016, 2017), non-epitheliotropic cutaneous lymphomas originating from T lymphocytes were the most commonly diagnosed, and included: anaplastic large T-cell lymphoma (ALTCL), peripheral nonspecific T-cell lymphoma (PTCL-NOS), and subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Less frequently, diffuse large B-cell lymphoma – immunoblastic variant (DLBCL), lymphomatoid granulomatosis (LYG) and marginal zone lymphoma (MZL) of MALT – lymphoplasmacytic variant were observed. Regarding the epidemiology of the cases diagnosed as non-epitheliotropic cutaneous lymphomas, the dogs were mainly purebred (13/18, 72.2%) and aged between two and 16 years, with a mean of 8.2 years, resembling what has been described for dogs with this form of cancer (Gross et al. 2005, Miller et al. 2013). However, regarding gender, a difference was observed between the existing information in the veterinary literature and the data obtained in this study, in which males were more frequently affected (12/18, 66.7%).

Regarding the macroscopic presentation, it was possible to note that ALTCL mostly occurs as multiple lesions, in the form of nodules or plaques, which may be alopecic and/or red to pink, usually ulcerated, and predominantly distributed in the ventral region of the body and limbs. This multiple pattern reflects the rapidly progressive characteristic attributed to this form of cancer in dogs, which often progresses with systemic involvement (Valli et al. 2016, Azuma et al. 2021), as can be observed in the two necropsied dogs with this presentation. Considering that there are few studies about the post-diagnosis biological behavior of the cutaneous form of ALTCL, the malignancy of the condition has been mainly grounded on the anaplasia of neoplastic lymphocytes which, by definition, denotes its aggressive nature (Valli et al. 2017, Azuma et al. 2021). Differently, in humans, despite its malignant morphological character, when it originates from the skin, ALTCL usually presents a favorable prognosis, and

is even recognized as "obsolete lymphoma" because it occurs in the form of solitary lesions that can regress spontaneously (Cerroni 2014a, Swerdlow et al. 2017).

PTCL-NOS corresponds to a group of lymphomas that, based on histopathology alone, cannot be fully characterized and classified (Valli 2007b, Swerdlow et al. 2017, Valli et al. 2017). In human medicine, through the use of immunohistochemical profiling and cytogenetic assessment, to date, three primarily cutaneous entities have been characterized under this designation (Cerroni 2014d, Magro et al. 2016a, Swerdlow et al. 2017). However, for animals, in view of the limited availability of economic resources and further considering the infrequency with which cutaneous lymphomas occur in canine species, this characterization has been done more slowly and the generic diagnosis of PTCL-NOS has been applied (Valli 2007b, Valli et al. 2017). In this study, PTCL-NOS was predominantly represented by solitary, ulcerated skin lesions seen as nodules or plaques, located on the trunk or limbs, unlike humans, in which multiple presentation is generally the most common (Swerdlow et al. 2017). On histopathology, all cases were formed by a monomorphic neoplastic population, making it evident that, although this diagnosis suggests some variability, the types of lymphoma included in this group, present similar characteristics, such as cell size and mitosis rate (Valli 2007b, Swerdlow et al. 2017, Valli et al. 2017).

As for SPTCL, it was possible to note that lesions can be solitary or multiple, however, subcutaneous nodules predominated, and were mainly located on the trunk, similar to what has been previously described for dogs (Valli et al. 2016, Noland et al. 2018), but somewhat different from the human presentation, which includes the limbs as the most frequently affected sites (Cerroni 2014e, Magro et al. 2016b, Valli et al. 2017). While for humans SPTCL courses with good prognosis, integrating the group of lymphomas characterized as indolent, in dogs, its biological behavior seems to be more aggressive (Noland et al. 2018). This assumption was suggested in a study conducted by Noland et al. (2018), in which most dogs with this form of cancer presented, at the time of diagnosis, multiple or solitary lesions, but that quickly evolved to generalized cutaneous involvement, even under treatment. In our study, similarly, the malignancy of SPTCL became evident by the advanced stage of lesions observed in most cases, with multiple subcutaneous involvement and focally extensive and ulcerated mass lesion.

DLBCL is in general the most commonly diagnosed histological type of lymphoma in dogs, including the centroblastic and immunoblastic variants as the most frequent (Ponce et al. 2010, Valli et al. 2011, 2017). However, the primarily tegumentary presentation is considered rare, with only one reported case in the literature involving the subcutaneous tissue of a dog (Cortina et al. 2020). In this case, Cortina et al. (2020) described subcutaneous lesions mostly located on the trunk, resembling the distribution pattern observed in the two cases diagnosed as DLBCL in our study. In dogs, this form of cancer is clinically mostly seen as generalized nodal involvement that in the late stage of the disease can metastasize to any organ or tissue, including the skin (Valli et al. 2013, 2017). In view of this, we describe two cases of DLBCL originating from the subcutaneous tissue, since the lesions are unlikely to be metastatic, considering that they were multiple and/or extensive and that there was solitary nodal involvement.

LYG is an angiocentric, angiodestructive form of lymphoma rarely described in dogs (Valli 2007a, Valli et al. 2017). However, when it does occur, it primarily affects the lungs and less frequently the skin (Fitzgerald et al. 1991, Smith et al. 1996, Valli 2007a, Magi et al. 2009, Shimazaki et al. 2010, Valli et al. 2017). Despite the rarity with which this form of lymphoma is described in dogs, when it involves the skin, multiple skin lesions, in the form of crateriform ulcers or of papules and nodules, seem to be more common (Smith et al. 1996, Gross et al. 2005, Shimazaki et al. 2010), but solitary lesions may occur, as was observed in the only case diagnosed as LYG in this study. In human medicine, the occurrence of LYG has been associated with Epstein-Barr Virus infection affecting immunocompromised individuals, however, in dogs, no viral infection influence has been established to date (Cerroni 2014b, Swerdlow et al. 2017, Valli et al. 2016).

MLZ of MALT is a rare condition in dogs, which is corroborated by the small number of descriptions in the literature including salivary glands, tonsils, nictitating membrane, lungs, intestines, and uterus as primarily involved sites, with no reports of cutaneous involvement (Valli 2007a, Ponce et al. 2010, Hong et al. 2011, Ko et al. 2013, Valli et al. 2016). However, in human medicine it is considered one of the main B-cell originating lymphomas occurring in the skin, usually seen as a dermal and variably heterogeneous neoplastic lymphoid population in a nodular pattern, but which can also be diffuse (Swerdlow et al. 2017). The histological presentation most commonly seen in humans with this form of cancer is termed "conventional variant", and is characterized by a mixed neoplastic population of marginal zone cells, lymphoplasmacytoid lymphocytes, and plasma cells, with small reactive T lymphocytes or germinal center remnants (Dalle et al. 2010, Cerroni 2014c, Swerdlow et al. 2017). Less frequently, the "lymphoplasmacytic variant" of monomorphic, diffuse neoplastic population predominantly in lymphoplasmacytic lymphocytes can be observed, similarly to what was seen in the case included in this study (Dalle et al. 2010, Cerroni 2014c). The diagnosis was made based on the morphological and immunophenotypic characteristics of the neoplastic cells, considering that B-cell lymphomas with plasmacytic differentiation or plasmacytomas do not present immunolabeling for Pax5 (Ramos-Vara & Borst 2017), then allowing the exclusion of these differential diagnoses. Therefore, this case represents the first description of a cutaneous MZL of MALT in a dog.

CONCLUSIONS

Based on the pathology findings obtained from this study it is possible to infer that when faced with a suspicion of non-epitheliotropic cutaneous lymphoma in a dog, when encountering multiple cutaneous lesions, nodular or placoid and predominant on trunk and limbs, it is more likely that the histopathological diagnosis will be consistent with ALTCL. On the other hand, when faced with solitary cutaneous nodules or plaques, PTCL-NOS will be the most often observed histologic type.

When including lymphoma as a differential diagnosis for dogs presenting mainly single or multiple nodules and plaques in subcutaneous tissue, one should first think of SPTCL. More rarely, DLBCL is a diagnosis to be considered,

but only when the lesions have a red or pink cut surface, since in cases of SPTCL they are predominantly white. With regard to epitheliotropic cutaneous lymphomas, the cutaneous form of mycosis fungoides is the most commonly seen in dogs, particularly in the premycotic and mycotic phases.

We hope this information will assist clinical veterinarians and pathologists in their diagnostic routines, as well as contribute to the characterization of non-epitheliotropic cutaneous lymphomas in the canine species.

Authors' contributions.- Renata D. Mazaro was responsible for performing the autopsies, preparation and staining of histological slides, immunohistochemistry, histopathological evaluation and preparation of the manuscript. Douglas M. Lorenzetti assisted the first author in performing the autopsies, as well as in the preparation and staining of histological slides for reevaluation and classification of cases. Suzana M.G. Leite collaborated with cases of her routine, providing the respective paraffin blocks and macroscopic photos. Eduardo K. Masuda collaborated with cases of his routine, providing the respective paraffin blocks and macroscopic photos. Leonardo D. Da Costa collaborated with cases of his routine, providing the respective paraffin blocks and macroscopic photos. Rosemeri O. Vasconcelos collaborated with cases from the routine of the Laboratory of Veterinary Histopathology, Unesp, Jaboticabal, providing the respective paraffin blocks and macroscopic photos. Antonio Flávio M. Dantas collaborated with cases from the routine of the Laboratory of Animal Pathology, UFCG, providing the respective paraffin blocks and macroscopic photos. Luciana C. Lacerda collaborated with cases of her routine, providing the respective paraffin blocks and macroscopic photos. Tereza Cristina Da Silva assisted the first author in the preparation of slides for immunohistochemistry, as well as in the execution of the technique. Marco Aurélio A. Motta collaborated with cases of his routine, providing biopsy specimens for histopathological diagnosis, as well as macroscopic photos of the respective cases. Bruno Cogliati provided the antibodies, as well as all the necessary inputs for the IHC technique, which was performed in the Morphological and Molecular Pathology Laboratory of FMVZ-USP, and also guided the first author in the evaluation of the slides submitted to IHC. Rafael A. Fighera was the advisor of the first author in the Laboratory of Veterinary Pathology of UFSM. Supervised the necropsies, histological and immunohistochemical evaluation and classification of all cases, and the preparation of the manuscript.

Acknowledgments.- The authors thank the "Conselho Nacional de Desenvolvimento Científico e Tecnológico" (CNPq) and the "Coordenação de Aperfeiçoamento de Pessoal de Nível Superior" (CAPES) for granting graduate scholarships.

Conflict of interest statement.- The authors declare no conflict of interests.

REFERENCES

Azuma K., Ohmi A., Goto-Koshino Y., Tomiyasu H., Ohno K., Chambers J.K., Uchida K., Namba H., Nagata M., Nagamine E., Nibe K., Irie M. & Tsujimoto H. 2021. Outcomes and prognostic factors in canine epitheliotropic and nonepitheliotropic cutaneous T-cell lymphomas. Vet. Comp. Oncol. 20(1):118-126. <https://dx.doi.org/10.1111/vco.12752> <PMid:34250731>

Cerroni L. 2014a. Cutaneous anaplastic large cell lymphoma, p.99-108. In: Cerroni L. (Ed.), Skin Lymphoma – The Illustrated Guide. 4th ed. Wiley Blackwell, Oxford.

Cerroni L. 2014b. Cutaneous lymphomatoid granulomatosis, p.253-255. In: Cerroni L. (Ed.), Skin Lymphoma – The Illustrated Guide. 4th ed. Wiley Blackwell, Oxford.

Cerroni L. 2014c. Cutaneous marginal zone lymphoma (cutaneous MALT-lymphoma) and variants, p.201-219. In: Cerroni L. (Ed.), Skin Lymphoma – The Illustrated Guide. 4th ed. Wiley Blackwell, Oxford.

Cerroni L. 2014d. Cutaneous peripheral T-cell lymphoma, not otherwise specified (NOS), p.155-162. In: Cerroni L. (Ed.), Skin Lymphoma – The Illustrated Guide. 4th ed. Wiley Blackwell, Oxford.

Cerroni L. 2014e. Subcutaneous panniculitis-like T-cell lymphoma, p.120-132. In: Cerroni L. (Ed.), Skin Lymphoma – The Illustrated Guide. 4th ed. Wiley Blackwell, Oxford.

Cortina B., Guenthner E. & Sypniewski L. 2020. Subcutaneous B cell lymphoma in a dog from the West Indies. Case Rep. Vet. Med. 25:1-5. <https://dx.doi.org/10.1155/2020/3695130> <PMid:32047701>

Dalle S., Thomas L., Balme B., Dumontet C. & Thieblemont C. 2010. Primary cutaneous marginal zone lymphoma. Crit. Rev. Oncol. Hematol. 74(3):156-162. <https://dx.doi.org/10.1016/j.critrevonc.2009.09.003> <PMid:19819717>

Fighera R.A., Souza T.M., Schmidt C. & Barros C.S.L. 2003. Micose fungóide em um cão. Clin. Vet. 45:34-38.

Fitzgerald S.D., Wolf D.C. & Carlton W.W. 1991. Eight cases of canine lymphomatoid granulomatosis. Vet. Pathol. 28(3):241-245. <https://dx.doi.org/10.1177/030098589102800308> <PMid:1858255>

Fontaine J., Bovens C., Bettenay S. & Mueller R.S. 2009. Canine cutaneous epitheliotropic T-cell lymphoma: a review. Vet. Comp. Oncol. 7(1):1-14. <https://dx.doi.org/10.1111/j.1476-5829.2008.00176.x> <PMid:19222826>

Fontaine J., Heimann M. & Day M.J. 2010. Canine cutaneous epitheliotropic T-cell lymphoma: a review of 30 cases. Vet. Comp. Oncol. 21(3):267-275. <https://dx.doi.org/10.1111/j.1365-3164.2009.00793.x> <PMid:20141606>

Goldschmidt M.H. & Shofer F.F. 1992. Cutaneous lymphosarcoma, p.252-264. In: Goldschmidt M.H. & Shofer F.F. (Eds), Skin Tumors of the Dog and Cat. 1ª ed. Pergamon Press, New York.

Gross T.L., Ihrke P.J., Walder E.J. & Affolter V.K. 2005. Part II: mesenchymal neoplasms and other tumors: lymphocytic tumors, p.866-893. In: Gross T.L., Ihrke P.J., Walder E.J. & Affolter V.K. (Eds), Skin Diseases of the Dog and Cat: clinical and histopathologic diagnosis. 2nd ed. Blackwell Science, Iowa.

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 and Sons, Ames. <https://dx.doi.org/10.1002/9781119181200.ch5>

Hong I.-H., Bae S.-H., Lee S.-G., Park J.-K., Ji A.-R., Ki M.-R., Han S.-Y., Lee E.-M., Kim A.-Y., You S.-Y., Kim T.-H. & Jeong K.-S. 2011. Mucosa-associated lymphoid tissue lymphoma of the third eyelid conjunctiva in a dog. Vet. Ophthalmol. 14(1):61-65. <https://dx.doi.org/10.1111/j.1463-5224.2010.00843.x> <PMid:21199281>

Ko J.S., Kim H.J., Han S. & Do S.H. 2013. Primary lymphoma of the uterine horn in a Lhasa Apso dog. Irish Vet. J. 66:24. <https://dx.doi.org/10.1186/2046-0481-66-24>

Magi G.E., DiPasquale S. & Renzoni G. 2009. Cutaneous lymphomatoid granulomatosis (angiotropic lymphoma) in a dog: immunophenotyping analysis. Vet. Res. Commun. 33(Supl.1):145-147. <https://dx.doi.org/10.1007/s11259-009-9264-x> <PMid:19578958>

Magro C.M., Crowson A.N. & Mihm Jr M.C. 2016a. CD4+ Peripheral T cell lymphoma, not otherwise specified, including primary cutaneous Cd4+ small/ medium-sized pleomorphic T cell lymphoma, p.312-333. In: Magro C.M., Crowson A.N. & Mihm Jr M.C. (Eds), The Cutaneous Lymphoid Proliferations: a comprehensive textbook of lymphocytic infiltrates of the skin. 2nd ed. Wiley Blackwell, Hoboken.

Magro C.M., Crowson A.N. & Mihm Jr M.C. 2016b. Subcutaneous panniculitis-like T cell lymphoma, p.334-350. In: Magro C.M., Crowson A.N. & Mihm Jr M.C. (Eds), The Cutaneous Lymphoid Proliferations: a comprehensive textbook of lymphocytic infiltrates of the skin. 2nd ed. Wiley Blackwell, Hoboken.

Mauldin E.A. & Peters-Kennedy J. 2016. Integumentary system, p.509-736. Maxie M.G. (Ed.), Jubb, Kennedy, and Palmer's Pathology of Domestic Animals. Vol.1. 6th ed. Elsevier, St. Louis. <https://dx.doi.org/10.1016/B978-0-7020-5317-7.00006-0>

Mazaro R.D., Luz F.S., Lorensetti D.M., Hartmann G. & Fighera R.A. 2019. Reticulose pagetoide em um cão: relato de caso. Arq. Bras. Med. Vet. Zootec. 71(3):883-888. <https://dx.doi.org/10.1590/1678-4162-10638>

Miller W.H., Griffin C.E. & Kirk K.C. 2013. Neoplastic and non neoplastic tumors, p.774-843. In: Miller W.H., Griffin C.E. & Kirk K.C. (Eds), Muller and Kirk's Small Animal Dermatology. 7th ed. Elsevier, St. Louis.

Moore P.F. & Olivry T. 1994. Cutaneous lymphomas in companion animals. Clin. Dermatol. 12(4):499-505. <https://dx.doi.org/10.1016/0738-081x(94)90216-x> <PMid:7866943>

Moore P.F., Affolter V.K. & Keller S.M. 2013. Canine inflamed nonepitheliotropic cutaneous T-cell lymphoma: a diagnostic conundrum. Vet. Dermatol. 24(1):204-e45. <https://dx.doi.org/10.1111/j.1365-3164.2012.01106.x> <PMid:23331699>

Moore P.F., Affolter V.K., Graham P.S. & Hirt B. 2009. Canine epitheliotropic cutaneous T-cell lymphoma: an investigation of T-cell receptor immunophenotype, lesion topography and molecular clonality. Vet. Dermatol. 20(6/7):569-576. <https://dx.doi.org/10.1111/j.1365-3164.2009.00814.x> <PMid:20178496>

Noland E.L., Keller S.M. & Kiupel M. 2018. Subcutaneous panniculitis-like T-cell lymphoma in dogs: morphologic and immunohistochemical classification. Vet. Pathol. 55(6):802-808. <https://dx.doi.org/10.1177/0300985818789474> <PMid:30071780>

Ponce F., Marchal T., Magnol J.P., Turinelli V., Ledieu D., Bonnefont C., Pastor M., Delignette M.L. & Fournel-Fleury C. 2010. A Morphological study of 608 cases of canine malignant lymphoma in France with a focus on comparative similarities between canine and human lymphoma morphology. Vet. Pathol. 47(3):414-433. <https://dx.doi.org/10.1177/0300985810363902> <PMid:20472804>

Ramos-Vara J.A. & Borst L.B. 2017. Immunohistochemistry: fundamentals and applications in oncology, p.44-87. In: Meuten D.J. (Ed.), Tumors in Domestic Animals. 5th. John Wiley and Sons, Ames. <https://dx.doi.org/10.1002/9781119181200.ch3>

Shimazaki T., Nagata M., Goto-Koshino Y., Tsujimoto H. & Shirota K. 2010. A case of canine lymphomatoid granulomatosis with cutaneous lesions. J. Vet. Med. Sci. 72(8):1067-1069. <https://dx.doi.org/10.1292/jvms.09-0479> <PMid:20234113>

Smith K.C., Day M.J., Schaw S.C., Littlewood J.D. & Jeffery N.D. 1996. Canine lymphomatoid granulomatosis: an immunophenotypic analysis of three cases. J. Comp. Pathol. 115(2):129-138. <https://dx.doi.org/10.1016/s0021-9975(96)80035-1> <PMid:8910741>

Souza T.M., Fighera R.A., Irigoyen L.F. & Barros C.S.L. 2006. Retrospective study of 761 cutaneous tumors in dogs. Ciência Rural 36(2):555-560. <https://dx.doi.org/10.1590/S0103-84782006000200030>

Swerdlow S.H., Campo E., Harris N.L., Jaffe E.S., Pileri S.A., Stein H., Thiele J. & Vardiman J.W. 2017. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Vol. 2. World Health Organization, Lyon. 441p

Valli V.E. 2007a. B-cell neoplasms, p.119-274. In: Valli V.E. (Ed.), Veterinary Comparative Hematopathology. 1st ed. Blackwell Publishing Ltd., Ames.

Valli V.E. 2007b. T-cell and NK-cell neoplasms, p.275-365. In: Valli V.E. (Ed.), Veterinary Comparative Hematopathology. 1st ed. Blackwell Publishing Ltd., Ames.

Valli V.E., Bienzle D., Meuten D.J. & Linder K.E. 2017. Tumors of the hemolymphatic system, p.203-321. In: Meuten D.J. (Ed.), Tumors in Domestic Animals. 5th ed. John Wiley and Sons, Ames. <https://dx.doi.org/10.1002/9781119181200.ch7>

Valli V.E., Jacobs R.M., Parodi A.L., Vernau W. & Moore P.F. 2002. World Health Organization International Histological Classification of Hematopoietic Tumors of Domestic Animals. Vol.8. Armed Forces Institute of Pathology American Registry of Pathology, Washington. 190p.

Valli V.E., Kass P.H., Myint M.S. & Scott F. 2013. Canine lymphomas: association of classification type, disease stage, tumor subtype, mitotic rate, and treatment with survival. Vet. Pathol. 50(5):738-748. <https://dx.doi.org/10.1177/0300985813478210> <PMid:23444036>

Valli V.E., Myint M.S., Barthel A., Bienzle D., Caswell J., Colbatzky F., Durham A., Ehrhart E.J., Johnson Y., Jones C., Kiupel M., Labelle P., Lester S., Miller M., Moore P., Moroff S., Roccabianca P., Ramos-Vara J., Ross A., Scase T., Tvedten H. & Vernau W. 2011. Classification of canine malignant lymphomas according to the World Health Organization criteria. Vet. Pathol. 48(1):198-211. <https://dx.doi.org/10.1177/0300985810379428> <PMid:20861499>

Valli V.E.O., Kiupel M., Bienzle D. & Wood R.D. 2016. Hematopoietic system, p.102-268. In: Maxie M.G. (Ed.), Jubb, Kennedy, and Palmer's Pathology of Domestic Animals. Vol.3. 6th ed. Elsevier, St. Louis. <https://dx.doi.org/10.1016/B978-0-7020-5319-1.00013-X>

Willemze R., Hodak E., Zinzani P.L., Specht L., Ladetto M. & on behalf of the ESMO Guidelines Working Group. 2013. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 24(Supl.6):vi149-vi154. <https://dx.doi.org/10.1093/annonc/mdt242> <PMid:23868906>