Acta Scientiae Veterinariae, 2024. 52(Suppl 1): 950.

CASE REPORT
Pub. 950

ISSN 1679-9216

Canine Ischemic Dermatopathy - Clinical and Laboratory Follow-up

Tiago Cunha Ferreira[1], Fábio Ranyeri Nunes Rodrigues[2], Hélio Noberto de Araújo Júnior[1], Carlos Donato Barbosa Alves Júnior[1] & Diana Célia Sousa Nunes-Pinheiro[1]

ABSTRACT

***Background*:** Canine ischemic dermatopathy poses an increasing challenge in Veterinary Dermatology, stemming from compromised cutaneous blood supply, resulting in skin lesions due to inadequate oxygen and nutrient delivery. Treatment strategies involve enhancing blood flow, pain management, and wound healing, necessitating vigilant monitoring of inflammatory control and therapy-related side effects. This study aims to present a comprehensive clinical and laboratory follow-up of 2 cases of canine ischemic dermatopathy.

***Cases*:** The 2 cases involved a 2-year-old Pitbull weighing 19.5 kg and a 3-year-old Mongrel bitch weighing 5.0 kg, both presenting widespread alopecic and crusting lesions. Blood samples were collected for hemato-biochemical (D0, D30 and D60 (case 1) and D0, D21 and D45 (case 2) and serological exams for Leishmaniasis, along with cutaneous cytology (ear tips) and biopsy for histopathological analysis. Hemato-biochemical analysis revealed leukocytosis with an elevated neutrophil count, and seronegativity to Canine Leishmaniasis. Cytological and histopathological analyses confirmed the diagnosis of canine ischemic dermatopathy, revealing a pyogranulomatous inflammatory process and characteristic skin alterations. Treatment strategies were customized for each case, with the Pitbull initially treated with pentoxifylline (10 mg/kg) and prednisolone (1.5 mg/kg) and later transitioned to oclacitinib (0.4 mg/kg), resulting in improved clinical signs and hemato-biochemical parameters. The Mongrel bitch exhibited substantial skin recovery and reduced inflammatory biomarker levels following oclacitinib (0.4 mg/kg) therapy.

***Discussion*:** The report offers a comprehensive account of the clinical and laboratory monitoring of 2 bitches with canine ischemic dermatopathy. The primary clinical hallmark of this ailment is the development of widespread alopecic and crusted lesions, prompting diagnostic consideration in the patient under discussion, supported by the clinical history and complementary examinations. Histological and cytological assessments confirmed the characteristics indicative of ischemic dermatopathy, while systemic leukocyte analysis highlighted an inflammatory state attributed to the skin lesions. Immunomodulators formed the basis of therapy in both cases. However, the Pitbull did not exhibit a complete clinical response, necessitating a transition from pentoxifylline to oclacitinib. Post-treatment hemato-biochemical evaluations demonstrated a gradual reduction in the systemic inflammatory process. Attention is drawn to the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and albumin to globulin ratio (AGR) as these cost-effective biomarkers offer insights less susceptible to pathophysiological variations compared to individual analyses. These parameters are increasingly recognized for their potential in monitoring chronic inflammatory diseases. Following clinical and hematological improvement, the frequency of oclacitinib was initially reduced from BID to SID. However, a recurrence of lesions prompted a reinstatement of oclacitinib in a BID regimen. This report presents a comprehensive clinical and laboratory follow-up of canine ischemic dermatopathy in 2 bitches and notably introduces the utilization of NLR, PLR, and AGR for monitoring therapeutic progression in this context. Encouragement is given for further studies and reports exploring the application of these biomarkers in monitoring this disease.

Keywords: canine ischemic diseases, bitch, neutrophil to lymphocyte ratio, systemic inflammation.

DOI: 10.22456/1679-9216.135947

Received: 18 October 2023 Accepted: 4 March 2024 Published: 24 April 2024

[1]Laboratório de Imunologia e Bioquímica Animal, Programa de Pós-Graduação em Ciências Veterinárias (PPGCV), Faculdade de Veterinária, Universidade Estadual do Ceará (UECE), Fortaleza, CE, Brazil. [2]Laboratório IFVET, Fortaleza. CORRESPONDENCE: T.C. Ferreira [tiago.cunha@uece.br]. Laboratório de Imunologia e Bioquímica Animal, PPGCV, Faculdade de Veterinária - UECE. Av. Dr. Silas Munguba n. 1700. Campus do Itaperi. Bloco C. CEP 60914703 Fortaleza, CE, Brazil.

INTRODUCTION

Canine ischemic dermatopathy is a dermatological condition of growing importance, characterized by compromised cutaneous blood supply, which can be attributed to various factors, including thromboembolic processes, arterial stenosis, vascular compression, and microcirculatory alterations [9,12]. The clinical manifestations of this condition range from erythema and pruritus to cutaneous ulcers and necrosis [1,10].

Diagnosing and treating canine ischemic dermatopathy present significant clinical hurdles. Accurate diagnosis often necessitates a multimodal approach, integrating histopathological analyses and comprehensive clinical evaluations [9,12]. Therapeutically, strategies focused on improving blood flow, pain management, and wound healing are pivotal in mitigating the adverse effects of this condition. Utilization of topical, systemic, and interventional therapies may help minimize tissue damage and restore cutaneous function [1,12].

A profound understanding of canine ischemic dermatopathy is essential for Veterinary Dermatology due to its escalating incidence and the associated diagnostic challenges. This case report aims to enhance the current scientific literature by presenting and analyzing 2 detailed clinical cases, shedding light on their clinical features, diagnostic approaches, and therapeutic interventions. Additionally, this study endeavors to further scientific understanding by introducing the use of specific inflammatory biomarkers, such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and albumin/globulin ratio (AGR), to monitor and elucidate the inflammatory state in dogs affected by ischemic dermatopathy.

CASES

Two bitches, a 2-year-old spayed Pitbull weighing 19.5 kg and a 3-year-old spayed Mongrel weighing 5.0 kg, exhibited extensive alopecic and crusted lesions, and a history of dermatological problems since the ages of 5 months and 1 year, respectively. The 1st dog exhibited signs of the disease following a vaccination protocol, while the onset of symptoms in the 2nd dog was not associated with any apparent triggering factor. Previous treatments with antibiotics, steroidal anti-inflammatories, and antifungals resulted in only partial improvement of the clinical lesions. The bitches also experienced frequent regurgitation.

During the dermatological examination, diffuse erythema and hemo-meliceric crusts were observed affecting the back, belly, face, ears, and limbs (Figure 1). An ulcerated lesion was noted at the ear tip, along with onychodystrophy and paronychia, alopecia, and erosions at the tail tip. In the general clinical examination, the bitches were active, with a temperature of 39.3°C (Pitbull) and 38.7°C (Mongrel), well-hydrated, and presented reactive submandibular lymph nodes. Blood samples were collected for hemato-biochemical (D0, D30 and D60 - case 1 and D0, D21 and D45 - case 2) and serological exams for Leishmaniasis, along with cutaneous cytology (ear tips) and biopsy for histopathological analysis.

The hemato-biochemical analysis demonstrated an elevation in absolute neutrophil count. The detailed inflammatory parameters are outlined in Table 1 for comprehensive assessment. Cytological examination revealed a pyogranulomatous inflammatory process with a sparse presence of bacterial cells.

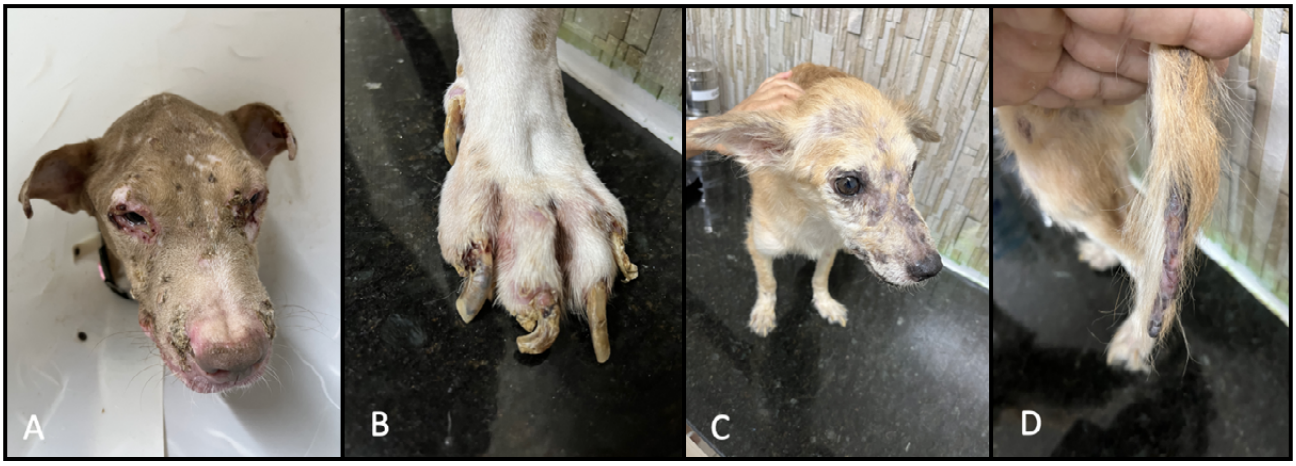

Figure 1. Canine patient affected by Canine Ischemic Dermatopathy. A- General clinical condition of the Pitbull, presenting periocular lesions, alopecic areas on the face, vasculopathy at the ear tip, and several foci of hemomeliceric crusts. B- Onychodystrophy and paronychia present in the Pitbull. C- Alopecic lesions in the facial region of the Mongrel. D- Vasculopathy at the tail tip in the Mongrel.

Table 1. Timeline of laboratory test results of bitches affected by canine ischemic dermatopathy.

	Case 1			Case 2		
Parameters	D0	D30	D60	D0	D21	D45
Neutrophils (/µL)	18,377	16,376	10,540	16,268	7,520	7,200
Lymphocyte (/µL)	2,591	2,320	1,800	2,156	1,830	1,900
Platelets (/µL)	489,000	320,000	295,000	688,000	280,000	315,000
NLR	7.09	7.05	5.85	7.54	4.10	3.78
PLR	188.7	137.9	163.8	319.1	153	165.78
Albumin (g/dL)	3.1	3.0	3.2	2.8	2.9	2.9
Globulin (g/dL)	6.7	6.1	4.9	5.7	5.1	3.9
AGR	0.46	0.49	0.65	0.49	0.56	0.76

Furthermore, histopathological analysis exhibited distinctive features, including interface dermatitis linked to atrophy of cutaneous appendages, accompanied by a discreet inflammatory infiltrate predominantly comprising lymphocytes and plasma cells (Figure 2). Collectively, these results strongly indicate the diagnosis of canine ischemic dermatopathy [1,4].

Based on these results, a therapeutic plan for Pitbull was initiated, involving pentoxifylline [Proex®[1] - 10 mg/kg, SID] and prednisolone [Alcort®)[1] - 1.5 mg/kg, SID], to induce treatment for the disease. Additionally, baths with 3% chlorhexidine shampoo [Hexadene®[2]] were administered to prevent secondary bacterial infections. Thirty days post-therapy, the bitch showed a partial improvement in skin lesions. A decision was made to prolong the treatment, with a reevaluation after 14 days to determine whether to maintain or change the medication. After the 14-day period, the patient returned with persistent inflammatory foci (Figure 3). Hence, a switch from pentoxifylline to oclacitinib [Apoquel®[3] - 0.4 mg/kg, BID], which significantly improved the dermatological lesions after 30 days of treatment.

In the case of the Mongrel bitch, the therapeutic regimen entailed administering oclacitinib [0.4 mg/kg, BID]. Concurrently, bathing using a 3% chlorhexidine shampoo [Hexadene®[2]] was implemented to mitigate the risk of secondary bacterial infections. Subsequently,

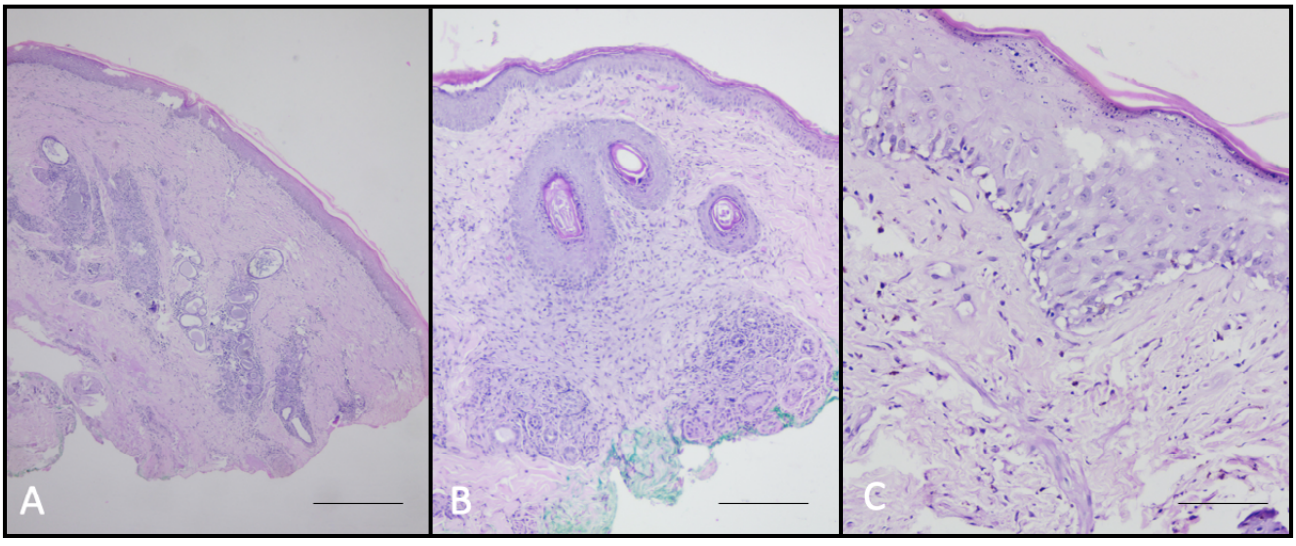

Figure 2. Histopathological aspects of pustule in a bitch patient with ischemic dermatopathy (H&E). A- Significant fibrosis with loss of appendages and ectasia of apocrine glands (40x). B- Compact orthokeratosis extending to the follicles. Within the dermis, fibrosis and a cluster of atrophic follicles are observed (100x). C- Dense orthokeratosis. Vacuolization and degeneration of basal layer cells. Slight chronic infiltration with discreet pigment incontinence (400x). [Scale bar= 50 µm].

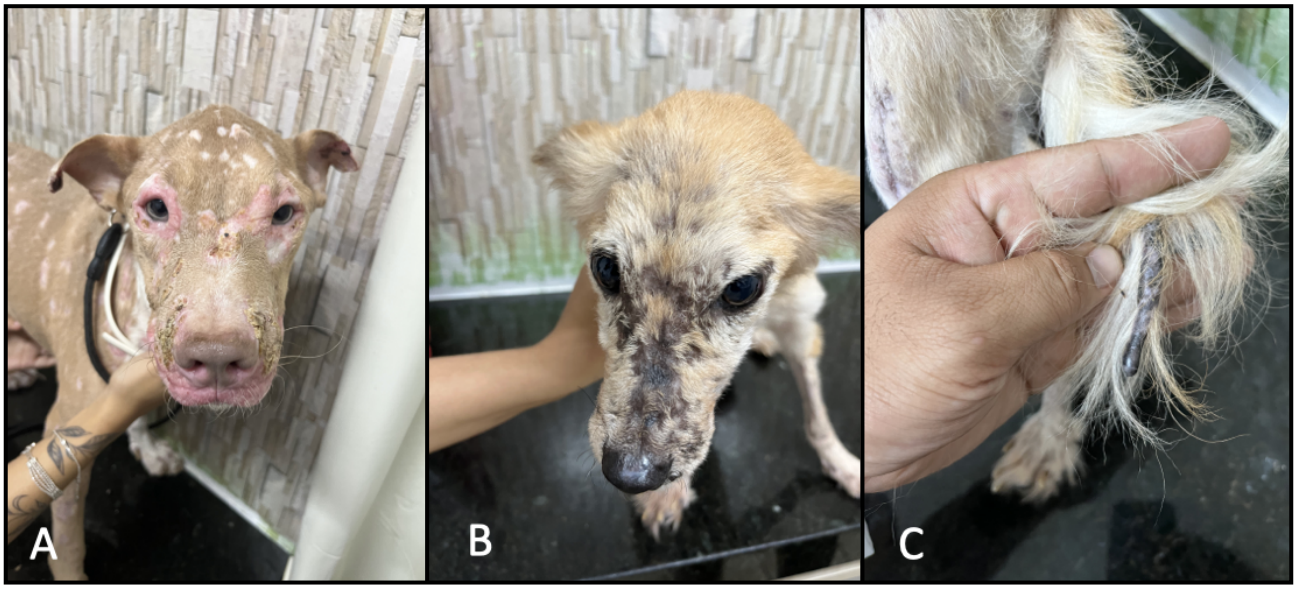

Figure 3. Clinical and dermatological features of canines with ischemic dermatopathy, 45 days after the initiation of immunomodulatory therapy. A- Persistence of inflammatory foci in the facial region, as well as hemomeliceric crusts (Pitbull). B & C- Clinical aspects of the canine patient (Mongrel) post-therapy, demonstrating slight re-epithelialization and control of the inflammatory process in the tail tip region.

notable improvements were observed in the dermatological lesions (Figure 3) and hemato-biochemical parameters, alongside a reduction in regurgitation episodes and a positive weight gain trajectory. Both bitches remain under an ongoing treatment protocol involving oclacitinib. It is worth noting that attempts to reduce the dosage led to a recurrence of cutaneous lesions, underscoring the necessity for a sustained therapeutic approach with oclacitinib.

DISCUSSION

Canine ischemic dermatopathy is an increasingly acknowledged dermatological condition within veterinary medicine, characterized by compromised cutaneous blood supply, resulting in insufficient oxygen and nutrient delivery to the skin. The resultant clinical manifestations span from erythema and pruritus to cutaneous ulcers and necrosis, which can affect regions from the face to the tail of the animal [1,10,12]. In the presented cases, both bitches exhibited erosive and ulcerative conditions consistent with ischemic dermatopathy and underwent targeted diagnostic procedures for this condition.

This immune-mediated disease has relatively unknown characteristics. Typically, the development of lesions is linked to triggering factors such as infections, vaccines, drugs, UV radiation, and stressful events [12]. In the cases under consideration, only the Pitbull had an event potentially associated with the development of lesions, as clinical signs began after completion of the puppy vaccination protocol. Although this event could be a potential trigger [17], it is believed that vaccines are just one component of the immunopathogenic process, given that previous studies have not definitively established a causative relationship [1].

Achieving precise diagnosis often necessitates a multimodal approach, encompassing thorough clinical evaluations, hemato-biochemical assessments, serological examinations, cutaneous cytology, and histopathological analysis [1,5,15]. In our cases, histopathological analysis unveiled distinctive features of interface dermatitis linked to atrophy of cutaneous appendages, substantiating the diagnosis of canine ischemic dermatopathy [1,4]. Additionally, given that the animals resided in an endemic area for canine leishmaniasis, it was pivotal to screen for this parasitic disease through serological tests. During this assessment, the animals tested seronegative.

Regarding hematological and biochemical findings, an elevation in neutrophil and lymphocyte counts was correlated with the inflammatory process induced by the disease, concomitant with a decline in albumin levels. Moreover, both bitches experienced recurrent regurgitation episodes, and the reduced albumin levels could potentially be attributed to nutritional deficiencies. These regurgitations might be associated with a megaesophagus condition secondary to ischemic dermatopathy, considering the possibility

of this disease affecting the musculature involved in swallowing [2]. Nevertheless, radiographic examinations are crucial for confirming the diagnosis, and further investigations are warranted to substantiate this hypothesis.

The therapeutic management of canine ischemic dermatopathy focuses on enhancing blood flow, alleviating pain, and facilitating wound healing [10]. In the cases presented, two primary therapeutic agents were employed: pentoxifylline and oclacitinib. Pentoxifylline, a methylxanthine derivative, possesses vasodilatory and anti-inflammatory properties, aiming to augment blood flow and mitigate inflammation [13]. Nevertheless, in the case of the Pitbull, the initial treatment with pentoxifylline yielded only partial improvement, necessitating a transition to oclacitinib.

Oclacitinib, a Janus kinase (JAK) inhibitor, was administered in both cases and demonstrated superior efficacy in managing dermatological lesions. This aligns with prior research [5,10], underscoring oclacitinib's effectiveness in treating pruritus and inflammation associated with immune-mediated skin conditions in canines. The prompt amelioration observed with oclacitinib in the presented cases highlights its potential as a valuable therapeutic option for canine ischemic dermatopathy, warranting further investigation.

The divergent therapeutic responses noted in the Pitbull case can likely be attributed to variances in the mechanisms of action of the administered medications. Pentoxifylline operates as a TNF-α inhibitor [13], modulating its pathway, while oclacitinib exerts its effects through selective inhibition of Janus Kinase [8], thereby substantially disrupting the signaling cascade of pro-inflammatory cytokines. Moreover, there is a hypothesis suggesting a potential correlation between a lower dosage of Pentoxifylline and a partial clinical response. This notion is supported by the broad range of reported doses in the literature [1].

The regulation of inflammation linked to drug administration could be systematically tracked through a sequential evaluation of hematological and biochemical parameters. Notably, in this regard, we underscore the significance of specific hematological ratios - NLR, PLR and AGR - for providing pivotal insights into the inflammatory milieu [6,7,14,16,18] and the subsequent response to treatment in cases of canine ischemic dermatopathy.

The NLR, reflective of the equilibrium between pro-inflammatory and anti-inflammatory processes, holds notable significance. Elevated NLR levels are frequently concurrent with an escalated inflammatory state, signifying a potential gauge for disease severity and treatment effectiveness [6,11]. Tracking alterations in the NLR over the treatment duration yielded crucial insights into the evolving inflammatory response, notably in the Pitbull case, enabling informed adjustments in therapeutic strategies.

Similarly, the PLR assumes significance, as platelets play a crucial role in the inflammatory cascade and tissue repair. An elevated PLR in dogs with ischemic dermatopathy may imply an enhanced inflammatory burden and a potential association with thrombotic or ischemic events [14,16]. Notably, in both cases, a reduction in PLR was observed concomitant with clinical improvement, underscoring the potential utility of PLR as a dynamic marker of response to therapy and disease amelioration.

Furthermore, the AGR, reflecting the nutritional and inflammatory status of the dog, holds diagnostic relevance. A decreased AGR can suggest malnutrition and an exacerbated inflammatory state, since albumin is a negative acute-phase protein [3]. The inversed AGR potentially affecting the overall prognosis and response to treatment [7,18]. Monitoring the AGR provided insights into the inflammatory progression in both cases, offering valuable insights for interventions in both clinical cases.

Lastly, the administration of oclacitinib demonstrated an association with a decrease in regurgitation episodes and a positive weight gain trend in the Mongrel dog. This observation hints at potential supplementary advantages of oclacitinib extending beyond its dermatological impacts, potentially influencing systemic inflammatory responses linked to canine ischemic dermatopathy. The sustained amelioration observed with oclacitinib, alongside the reappearance of clinical manifestations subsequent to a dose reduction, emphasizes the importance of maintaining an uninterrupted therapeutic regimen with this medication.

In conclusion, canine ischemic dermatopathy represents a significant challenge in veterinary dermatology, highlighting the importance of effective diagnostic and therapeutic approaches. Notably, oclacitinib has demonstrated remarkable efficacy in treating dermatological lesions associated with this condition. Moreover,

hematological ratios, including NLR, PLR, and AGR, provide valuable insights into inflammatory status and treatment response. Looking ahead, further research is essential to optimize therapeutic strategies, refine our understanding of these hematological indicators, and advance the management of canine ischemic dermatopathy, ultimately leading to improved patient outcomes.

MANUFACTURERS

[1]Cepav Pharma Ltda. São Paulo, SP, Brazil.
[2]Virbac do Brasil Indústria e Comércio Ltda. São Paulo, SP, Brazil.
[3]Zoetis Indústria de Produtos Veterinários Ltda. Campinas, SP, Brazil.

***Declaration of interest*.** The authors declare no conflicts of interest. The authors were responsible for the content and writing of the paper.

REFERENCES

1 **Backel K.A., Bradley C.W., Cain C.L., Morris D.O., Goldschimidt K.H. & Mauldin E.A. 2019.** Canine ischaemic dermatopathy: a retrospective study of 177 cases (2005-2016). *Veterinary Dermatology*. 30: 406-e122. DOI: 10.1111/vde.12772.

2 **Bresciani F., Zagnoli L., Fracassi F., Bianchi E., Cantile C., Abramo F. & Pietra M. 2014.** Dermatomyositis-like disease in a rottweiler. *Veterinary Dermatology*. 25: 229-262. DOI: 10.1111/vde.12128.

3 **Cagnasso F., Borrelli A., Bottero E., Benvenuti E., Ferriani R., Marchetti V., Ruggiero P., Bruno B., Maurella C. & Gianella P. 2023.** Comparative evaluation of peripheral blood neutrophil to lymphocyte ratio, serum albumin to globulin ratio and serum c-reactive protein to albumin ratio in dogs with inflammatory protein-losing enteropathy and healthy dogs. *Animals*. 13: 1-11. DOI: 10.3390/ani13030484.

4 **Conceição L.G. & Loures F.H. 2020.** Biópsia e histopatologia da pele. In: Larsson C.E. & Lucas R. (Eds). *Tratado de Medicina Externa - Dermatologia Veterinária*. 2.ed. São Caetano do Sul: Interbook Editorial, pp.145-167.

5 **Cousandier G., Scholten A.D., Scotton G. & Stefanello C. 2021.** Dermatopatia isquêmica juvenil em um cão. *Acta Scientiae Veterinariae*. 49: 1-7. DOI: 10.22456/1679-9216.105583.

6 **Ferreira T.C., Lima-Verde J.F., Silva Júnior J.A., Ferreira T.M.V., Viana D.A. & Nunes-Pinheiro D.C.S. 2021.** Analysis of systemic and cutaneous inflammatory immune response in canine atopic dermatitis. *Acta Scientiae Veterinariae*. 49: 1-8. DOI: 10.22456/1679-9216.109498.

7 **Ferreira T.M.V., Oliveira A.T.C., Carvalho V.M., Pinheiro A.D.N., Carvalho Sombra T.C.F., Ferreira T.C., Freitas J.C.C. & Nunes-Pinheiro D.C.S. 2021.** Leukocytes and albumin in canine leishmaniasis. *Acta Scientiae Veterinariae.* 49: 1-7. DOI: 10.22456/1679-9216.111869.

8 **Gonzales A.J., Bowman J.W., Fici G.J., Zhang M., Mann D.W. & Mitton-Fry M. 2014.** Oclacitinib (Apoquel®) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy. *Journal of Veterinary Pharmacology and Therapeutics*. 37: 317-324. DOI: 10.1111/jvp.12101.

9 **Innera M. 2013.** Cutaneous vasculitis in small animals. *Veterinary Clinics: Small Animal Practice*. 43: 113-134. DOI: 10.1016/j.cvsm.2012.09.011.

10 **Levy B.J., Linder K.E. & Olivry T. 2019.** The role of oclacitinib in the management of ischaemic dermatopathy in four dogs. *Veterinary Dermatology*. 30: 201-e63. DOI: 10.1111/vde.12743.

11 **Monteiro V.P., Oliveira A.T.C. & Ferreira T.C. 2020.** Pemphigus foliaceous in a dog - clinical and laboratorial assessment. *Acta Scientiae Veterinariae*. 48: 1-7. DOI: 10.22456/1679-9216.105171.

12 **Morris O. 2013.** Ischemic dermatopathies. *Veterinary Clinics: Small Animal Practice*. 43: 99-11. DOI: 10.1016/j.cvsm.2012.09.008.

13 **Queiroz Jr. C.M., Bessoni R.L.C., Costa V.V., Souza D.G., Teixeira M.M. & Silva T.A. 2013.** Preventive and therapeutic anti-TNF-α therapy with pentoxifylline decreases arthritis and the associated periodontal co-morbidity in mice. *Life Sciences*. 93: 423-428. DOI: 10.1016/j.lfs.2013.07.022.

14 **Rejec A., Butinar J., Gawor J. & Petelin M. 2017.** Evaluation of complete blood count indices (NLR, PLR, MPV/PLT, and PLCRi) in healthy dogs, dogs with periodontitis, and dogs with oropharyngeal tumors as potential biomarkers of systemic inflammatory response. *Journal of Veterinary Dentistry*. 34: 231-240. DOI: 10.1177/0898756417731775.

15 **Romero C., Garcia G., Sheinberg G., Cordero A., Rodrigues D. & Heredia R. 2018.** Three cases of canine dermatomyositis - like disease. *Acta Scientiae Veterinariae*. 46: 1-6. DOI: 10.22456/1679-9216.86435.

16 Sarkar S., Kannan S., Khanna P. & Singh A.K. 2022. Role of platelet-to-lymphocyte count ratio (PLR), as a prognostic indicator in COVID-19: a systematic review and meta-analysis. *Journal of Medical Virology*. 94: 211-221. DOI: 10.1002/jmv.27297.

17 Vitale B.C., Gross L.T. & Magro M.C. 1999. Vaccine-induced ischemic dermatopathy in the dog. *Veterinary Dermatology*. 10: 131-142. DOI: 10.1046/j.1365-3164.1999.00131.x.

18 Zhang J., Wang T., Fang Y., Wang M., Liu W., Zhao J., Wang B., Wu Z., Lv Y. & Wu R. 2021. Clinical significance of serum albumin/globulin ratio in patients with pyogenic liver abscess. *Frontiers in Surgery*. 8: 1-10. DOI: 10.3389/fsurg.2021.677799.