Acta Veterinaria Brasilica September 12 (2018) 76-83

Acta Veterinaria Brasilica

Journal homepage: https://periodicos.ufersa.edu.br/index.php/acta/index

Case Report

Clinical, laboratory and therapeutic aspects of canine idiopathic hypereosinophilic syndrome: case report

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A R T I C L E I N F O

Article history
Received 09 February 2018
Received in revised form 08 September 2018
Accepted 18 September 2018

Keywords:
Eosinophilia
Idiopathy
Internal medicine
Treatment
Canis familiaris

A B S T R A C T

The idiopathic hypereosinophilic syndrome (IHES) is a rare disease, characterized by variable eosinophilia and its massive infiltration into various organs. This study aimed to report clinical-laboratory findings and therapy in a canine with IHES. A one-year, 10-month-old male Rottweiler dog had a history of emesis, weight loss, hyporexia, and persistent eosinophilia on prior hematological exams. Vaccinations and worming were up to date. A complete blood count, serum biochemistry, bone marrow cytology, serology for leishmaniasis, chromatographic immunoassay for the detection of *Dirofilaria immitis* antigen, and abdominal ultrasound were requested. The tests for infectious diseases were negative. Blood biochemistry revealed no significant changes. An intense eosinophilia was observed in the hematology. A large number of cell precursors of the eosinophilic lineage were detected in the bone marrow cytology. Abdominal ultrasound showed thickening of intestinal loops. Considering the clinical and laboratory findings, the diagnosis of IHES was defined. Prednisolone treatment was instituted. The recurrence of peripheral eosinophilia occurred on the 35th day after therapy initiation. At that time, we opted to suspend the use of prednisolone and indicate the administration of deflazacort. With follow-up, therapeutic success with deflazacort was demonstrated, promoting the complete regression of clinical and ultrasound signs. The last glucocorticoid was maintained, but with a gradual dose reduction. The recognition of clinical and laboratory manifestations related to canine IHES is essential to establish an adequate diagnosis and therapy. Deflazacort emerges as a promising drug for controlling this disease.

INTRODUCTION

The idiopathic hypereosinophilic syndrome (IHES) is a condition described in humans, felines, ferrets, and more rarely in dogs (AROCH; PERL; MARKOVICS, 2001). It is characterized by a marked and persistent peripheral blood eosinophilia (GODOY et al., 2008). The condition is chronic and, for months, predisposes to the formation of eosinophilic inflammatory granulomas similar to tumors and eosinophil infiltrates in various organs and systems, and may be fatal (AROCH; PERL; MARKOVICS, 2001; GERMAN et al., 2002; GODOY et al., 2008).

Canines of the Rottweiler and German Shepherd breeds are the most affected because they present an exaggerated eosinophilic response to normal stimuli (LILLIEHOOK et al., 2000). The clinical signs manifested will depend on the affected organs (LILLIEHOOK; TVEDTEN, 2003).

The diagnosis is made by associating the clinical signs with laboratory findings, especially with a persistent eosinophilia in the blood count, excluding the main causes of eosinophilia. In addition to the other

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http://dx.doi.org/10.21708/avb.2018.12.3.7667

complementary tests may also assist in directing IHES diagnosis, such as bone marrow cytology and histopathology of the affected organs, as well as imaging tests (LILLIEHOOK; TVEDTEN, 2003).

The treatment, in general, is based on the use of immunosuppressive drugs, such as intermediate-acting corticosteroids, such as prednisolone and deflazacort (PERKINS; WATSON, 2001; BARRS et al., 2002; MACÊDO et al., 2016). Thus, this study aimed to report the clinical-laboratory findings and respective therapeutic management in a dog carrying IHES, in addition to praising the importance in differentiating with the common causes of eosinophilia in canine species.

CASE REPORT

A one-year, 10-month-old male Rottweiler dog was attended at the Veterinary Hospital of the Federal University of the Semi-Arid Region (Mossoró, Rio Grande do Norte, Brazil). The animal had a history of emesis, apathy, weight loss, and hyporexia, with the evolution of two months. There was a persistent eosinophilia in prior hematological exams. The dog was fed commercial feed ad libitum and was up to date with vaccination and worming protocols, the latter carried out 18 days ago with praziquantel, pyrantel pamoate, and febantel-based vermifuge. In addition, the dog had no contact with other animals or access to the street. There was also the report of previous treatments with prebiotics and vitamin supplements, but with no satisfactory response. The patient was submitted to a physical evaluation. Then, a complete blood count, serum biochemistry (alanine aminotransferase, alkaline phosphatase, total protein, and creatinine), urinalysis, bone marrow cytology, serology for leishmaniasis (using the techniques of indirect immunofluorescence and enzyme immunoassay), chromatographic immunoassay for the detection of *Dirofilaria immitis* antigen (in association with Knott test modified to check microfilariae), and abdominal ultrasound. We could not obtain radiographic images of the thoracic cavity.

Clinically, a thin nutritional status was observed (Figure 1A). Abdominal palpation revealed the presence of pain associated with intracavitary structures of significant thickening.

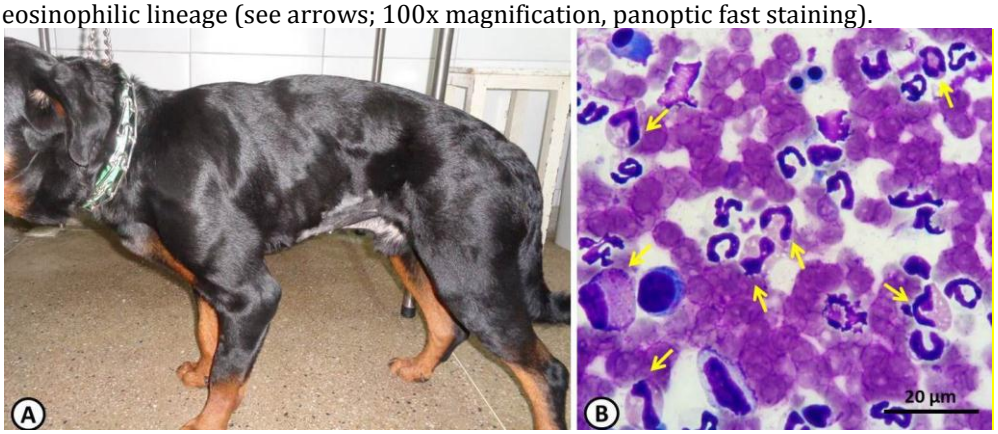
The tests for infectious diseases were negative. Blood biochemistry and urinalysis did not reveal significant changes. An intense eosinophilia was observed in the hematology (Table 1). The bone marrow cytology detected a hypercellularity, in association with a large number of cell precursors of the eosinophilic lineage, but with preservation of the usual morphological characteristics, with no sign of cellular atypia or neoplastic transformation (Figure 1B).

Table 1 – Relative and absolute values of the number of circulating eosinophils during the follow-up period of the one-year, 10-month-old male Rottweiler dog affected by IHES.

Days of treatment	Eosinophils	
	Relative (RV†: 2–10%)	Absolute (RV†: 120-1800/mm^3)
Day 0	19	5529
Day 12	1	292
Day 35	10	2550
Day 70	12	2268

RV†: reference value. Source: Personal archive.

Figure 1 – Clinical and cytological findings at the admission time of the one-year, 10-month-old male Rottweiler dog affected by IHES. A: thin nutritional status. B: photomicrography of the bone marrow evidencing a high number of cell precursors of the eosinophilic lineage (see arrows; 100x magnification, panoptic fast staining).



Source: Personal archive.

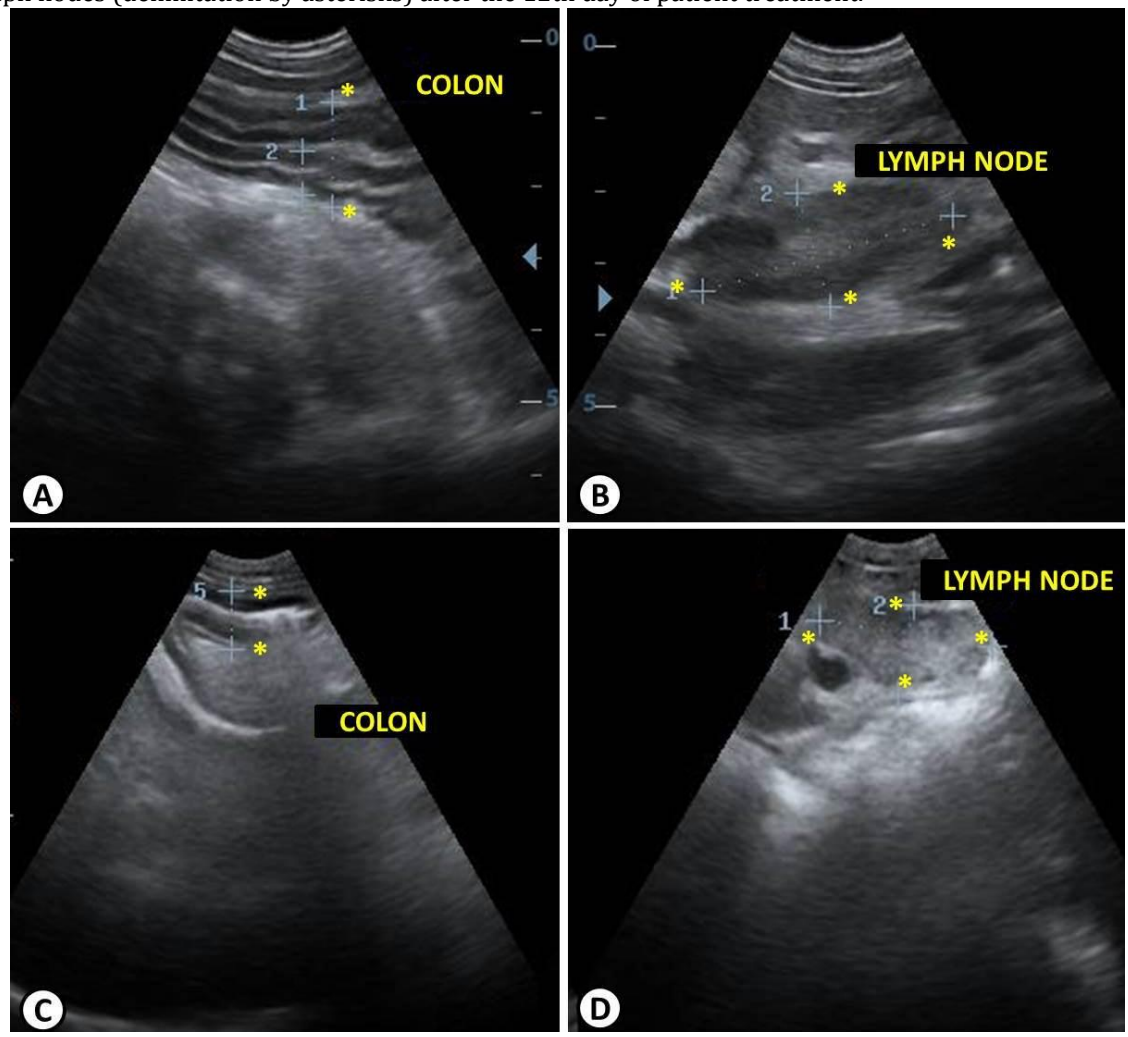
The abdominal ultrasound showed the colon wall thickening (1.26 cm), with loss of stratification of enteric layers, revealing a homogeneous echotexture (Figure 2A). Two defined, rounded, regular contour structures located in the epigastric region, both measuring approximately 8.2 × 1.8 cm, were also noted. The image was an indication of gastric lymph node hyperplasia (Figure 2B).

According to the clinical and laboratory findings, and in

agreement with the exclusion of other causes of eosinophilia, we reached the diagnosis of IHES. A prednisolone therapy (2 mg/kg, orally, every 24 hours) was instituted. Clinical and laboratory follow-up of the patient was performed.

Twelve days after treatment initiation, the canine presented alert behavior with normorexia and remission of emetic episodes, although without body weight gain. A decrease in the circulating amount of eosinophils was observed, falling within the absolute and relative reference range (Table 1). Serum biochemistry did not exhibit significant abnormalities. The eosinophil infiltrate in the bone marrow was still persistent, but with the previously identified morphological pattern. In the abdominal ultrasound, a reduction in colon thickness (0.8 cm) and persistence of structures in the epigastric area (but with regression of dimensions, which had an average value of 2.8 × 1.6 cm for both) was observed (Figures 2C and 2D).

Figure 2 – Ultrasonographic images of the one-year, 10-month-old male Rottweiler dog affected by IHES. A: colon wall thickening (delimitation by asterisks) at the time of patient admission. B: structures located in the epigastric region suggestive of gastric lymph node hyperplasia (delimitation by asterisks) at the time of patient admission. C: reduction of colon wall thickening (delimitation by asterisks) after the 12th day of patient treatment. D: regression of dimensions of the gastric lymph nodes (delimitation by asterisks) after the 12th day of patient treatment.



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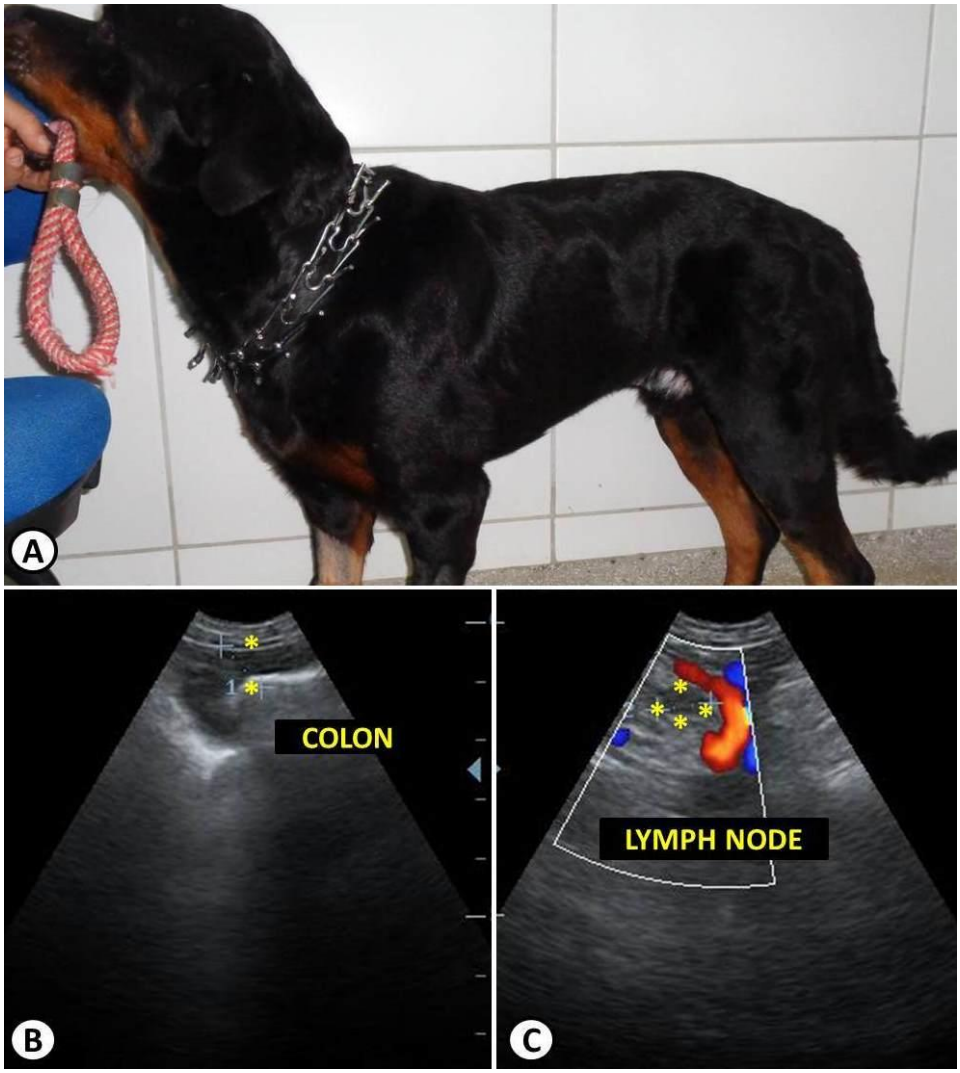
The dose of prednisolone was reduced (to 1 mg/kg) due to the progressive remission of clinical, hematological, and ultrasonographic changes, but maintaining the administration interval previously recommended.

Thirty-five days after therapy initiation, the animal exhibited an increase in body weight, with a clear visual perception (Figure 3A). The emetic episodes remained absent, but the dog presented alterations in the fecal score, in which the excrements, despite having texture, revealed indefinite forms with the presence of food residues and hematochezia points. Based on fecal macroscopy, a score of six was assigned (considering a scale ranging from one to seven). The recurrence of eosinophilia was observed in the hematology (Table 1). The findings of blood biochemistry and bone marrow

cytology were similar to the previous evaluation. The ultrasound of the abdominal cavity showed a reduction in both the colon wall thickness (0.74 cm) and the dimensions of the rounded structures (average value of 1.78 × 1.19 cm for both) (Figures 3B and 3C). Due to the recurrence of the systemic eosinophilia, the use of prednisolone was suspended, indicating the administration of deflazacort (0.3 mg/kg every 24 hours). The metronidazole (7.5 mg/kg every 12 hours) was also prescribed.

Figure 3 – Clinical and ultrasonographic findings after 35 days of treatment of the one-year, 10-month-old male Rottweiler dog affected by IHES. A: evident body weight gain. B: reduction of colon wall thickening (delimitation by asterisks) when compared to the previous ultrasonographic evaluation. C: regression of dimensions of the gastric lymph nodes (delimitation by asterisks) when compared to the previous ultrasonographic evaluation.



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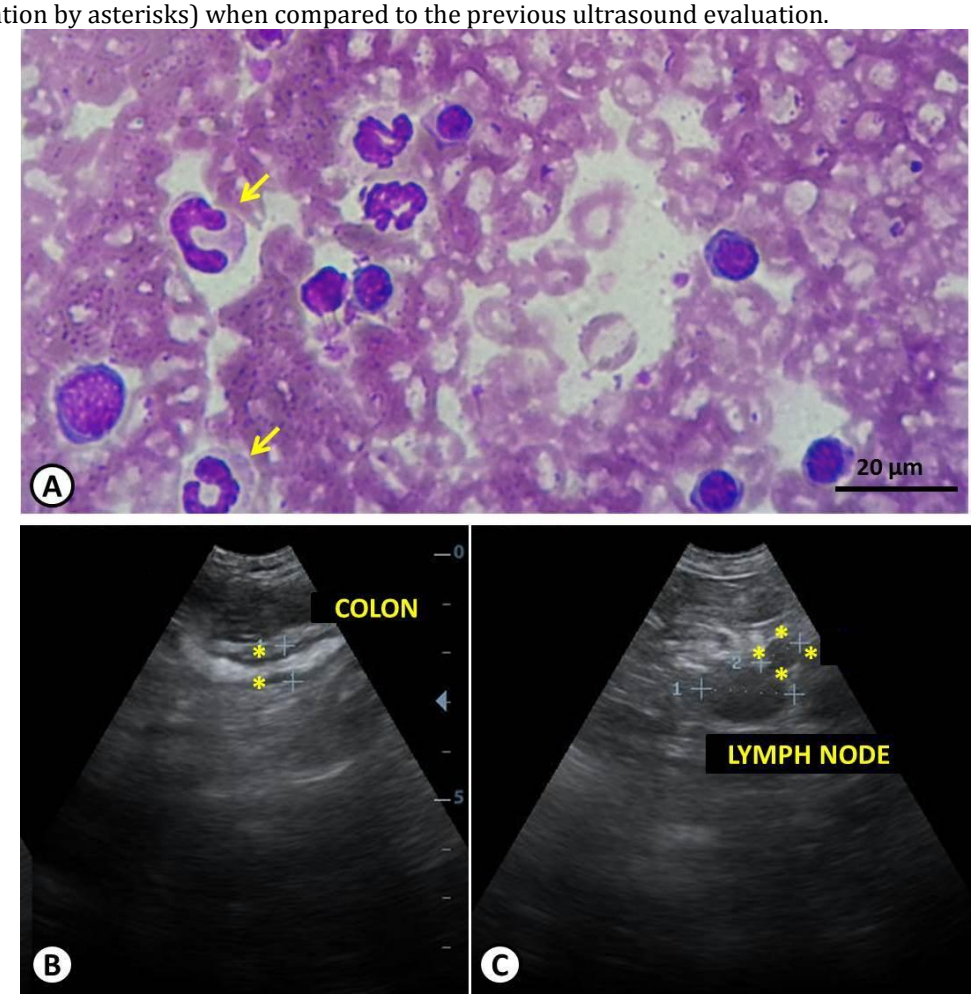
After 70 days of patient follow-up, a normal nutritional status was detected, with complete remission of enteric clinical signs and a normal defecation. No reports of vomiting were observed and the canid was in normorexia. There was the maintenance of peripheral eosinophilia, but with an absolute value lower than the previous blood count (Table 1) and with a reduction in the number of eosinophil precursors within the bone marrow (Figure 4A). Serum biochemistry showed an intense elevation of alkaline phosphatase (574 IU/L). The abdominal ultrasound revealed a colon wall thickness in the normal range, but still with persistence of intra-abdominal masses, with dimensions similar to that of the last imaging examination (Figures 4B and 4C). The discontinuation of metronidazole was recommended. A change in dose was indicated for deflazacort. The dose was initially reduced to 0.1 mg/kg, with the permanence of the previously recommended administration interval. Then, this dose was maintained, but with an expansion in the time of administration until the maintenance dose was obtained, which corresponded to 0.1 mg/kg every 72 hours.

Figure 4 – Cytological and ultrasonographic findings on the 70th day of follow-up of the one-year, 10-month-old male Rottweiler dog affected by IHES. A: photomicrography of the bone marrow evidencing a reduction in the number of cell precursors of the eosinophilic lineage (see arrows; 100x magnification, panoptic fast staining). B: colon wall showing an ultrasound thickness within the normality range (delimitation by asterisks). C: similarity of dimensions of the gastric lymph nodes (delimitation by asterisks) when compared to the previous ultrasound evaluation.



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DISCUSSION

The IHES was first described in humans in 1968 and was defined as a peripheral eosinophilia for more than six months (PERKINS; WATSON, 2001; SYKES et al., 2001). However, for canine species, based on data from the researched literature, this period has not yet been determined. For the described case, the evolution time of IHES was estimated to be at least three months, according to the patient's anamnesis information.

Although unusual, when IHES is diagnosed in dogs, a significantly higher frequency is usually observed for Rottweiler animals, as observed in the present report (PERKINS; WATSON, 2001; SYKES et al, 2001). This evidence is supported by a study of 105 canines with pronounced eosinophilia, of which 34% were Rottweiler (LILLIEHOOK et al., 2000). However, for IHES, there is no age or sex predisposition with evidence of genetic basis, but this hypothesis could not be considered for the canine under discussion because of its unknown origin (LILLIEHOOK et al., 2000; LILLIEHOOK; TVEDTEN, 2003).

In IHES, the exact pathophysiology for the exaggerated eosinophil production is still unknown, but interleukin-3, interleukin-5, and granulocyte-macrophage stimulating factor are known to have specific eosinophil and basophil receptors and may inhibit the apoptosis of eosinophilic elements (JAMES; MANSFIELD, 2009). The latter are cells well capable of tissue destruction and found in connective tissues of organs containing exogenous substances such as the skin, gastrointestinal, respiratory and urinary tract (RONCHI JUNIOR et al., 2010). The mobilization of eosinophils for a given site is mediated primarily by T helper 2 lymphocytes and mast cells, which release cytokines such as interleukin-3, interleukin-4, and interleukin-13, and the tumor necrosis factor, which will stimulate differentiation and proliferation in the bone marrow and promote eosinophil chemotaxis to the site where the inflammatory response was triggered. Therefore, when

an injury occurs at these sites, proteins with cytotoxic cationic granules are released, stimulating thrombosis, mast cell degranulation, releasing of oxygen free radicals, proinflammatory cytokines, and arachidonic acid-derived mediators (JAMES; MANSFIELD, 2009; RONCHI JUNIOR et al., 2010). However, these substances released during eosinophilic degranulation are not only capable of eliminating bacterial and parasitic infections but also lead to damage to adjacent tissues (SATTASATHUCHANA; STEINER, 2014). These mechanisms could justify the laboratory abnormalities and related clinical manifestations exhibited by the animal in evidence.

The clinical-laboratory findings common to all forms of canine IHES are equivalent to the relative and absolute peripheral eosinophilia, weight loss, dysphagia, emesis, abdominal pain, and diarrhea, with the gastrointestinal tract being one of the most frequently affected sites (RODRIGUEZ et al. 1995; NEIL et al., 2017). Such citations were in accordance with the context in question. The severity of the clinical condition is not directly related to peripheral eosinophilia but to the number of degranulated eosinophils in the tissues (RONCHI JUNIOR et al., 2010). Thus, for the reported canine, an intense invasion and eosinophilic activity may have occurred on the organs of the gastrointestinal tract at the time of patient admission since clinical, hematological, and ultrasonographic changes were evident and already demanded an extreme caution in its interpretation and management.

The thickening of the intestinal mucosa, with an irregular surface and nodulation formation, in addition to a reactive hyperplasia in regional lymph nodes can be observed in the abdominal ultrasound of dogs with IHES (RODRIGUEZ et al., 1995). These formations correspond to granulomas composed of mature and immature eosinophil infiltrates with notorious fibroplasia (FIGHERA et al., 2004). Thickening of the intestinal wall occurs when the submucosal and muscular layers are replaced by granulomatous tissue. The reactive lymph nodes also show a large eosinophil accumulation (JAMES; MANSFIELD, 2009). For the canid under discussion, the abnormalities present in the imaging diagnosis were directly correlated with the exhibited clinical signs. Firstly, the increased thickness of colon tunics, because of too much tissue infiltration of eosinophils, led to a probable cell degranulation and hence an inflammation of the gastrointestinal mucosa, resulting in the occurrence of emesis. Colon thickening (and the inflammation of its mucous membrane) could still have affected food assimilation, thus clarifying the reason for the chronic weight loss. The painful manifestation during the manipulation of the abdomen was based not only on the colic inflammatory process but also on the gastric lymphadenomegaly.

In this case, IHES led to predominant clinical manifestations of the gastrointestinal tract, with the involvement of the colon, evidenced by ultrasound examinations. Primary eosinophilic colitis would be a differential diagnosis for the canine condition. However, this disease, in addition to presenting a few reports in dogs, may not manifest peripheral eosinophilia (VAN DER GAAG; VAN DER LINDE-SIPMAN, 1987). Moreover, eosinophilic colitis has been reported in dogs with IHES (SATTASATHUCHANA; STEINER, 2014). Thus, the diagnosis of IHES was supported by clinical manifestations, persistent peripheral eosinophilia, and an intense involvement of bone marrow, which is not present in cases of primary eosinophilic enteropathies (SYKES et al., 2001; SATTASATHUCHANA; STEINER, 2014).

Other causes of peripheral and persistent eosinophilia in dogs need to be discarded prior to concluding the definitive diagnosis for IHES. The most common causes of eosinophilia in canine species include infestations by ectoparasites, chronic endogenous parasitism, either by intestinal parasites or those that run through the bloodstream, such as *Dirofilaria immitis*. It is also necessary to consider the relationship with diseases of infectious origin, such as visceral leishmaniasis, and neoplastic disorders, such as eosinophilic leukemia (LILLIEHOOK; TVEDTEN, 2003; MACEDO et al., 2016). In addition, dogs belonging to certain large breed patterns, especially Rottweilers and German Shepherds, have eosinophilia even though there are no parasitic, infectious, inflammatory or neoplastic changes, which is sometimes interpreted as "physiological eosinophilia" (NEIL et al., 2017). Therefore, for the animal of this study, the conjunction of information from anamnesis and the requested laboratory tests, with their correct interpretation and always considering diagnostic elimination criteria, allowed defining the IHES condition.

However, the search for the histological finding of eosinophilic infiltrate in the viscera and/or involved structures, in association with clinical-epidemiological aspects, blood, spinal and imaging alterations, in addition to the absence of underlying diseases, is recommended for the definitive IHES diagnosis (LILLIEHOOK; TVEDTEN, 2003; FIGHERA et al., 2004). Despite the lack of a histopathological analysis for the reported case, the congregation of epidemiological, clinical, hematological, cytological, and ultrasonographic data led to the diagnostic suspicion for IHES, which confirmation was obtained with satisfactory therapeutic results.

Glucocorticoids are the first-choice therapy, initially used in immunosuppressive doses, with the aim at reducing the implantation of eosinophils in the tissues and the viability time of this cell type, thus preventing damage to target organs (BARRS et al., 2002). Prednisolone acts negatively on interleukins and other factors that promote the perpetuation of eosinophils, in addition to

ameliorating their degranulation and quantity in the bloodstream, inhibiting tissue inflammation. Glucocorticoids are continuously used, with a gradual reduction in order to minimize the side effects (BARRS et al., 2002). In spite of the absence of histopathological evidence, in the present study, prednisolone invariably assisted in the suppression of chronic and active infiltration of eosinophils in the colon wall and inside the lymph nodes, with a partial (but significant) regression of the inflammatory and reactional process. One of the paradigms that corroborated this fact was the increase in body mass (secondary to an adequate absorption of nutrients after the supposed mechanical and functional restructuring of enteric mucosa), in association with the continuous attenuation in the ultrasonographic dimensions of the colon wall and gastric lymph nodes. However, the return of eosinophilia during the course of the therapy with prednisolone was probably due to the generation of the tachyphylaxis process, i.e. a reduction in the therapeutic response of the drug. This circumstance led to a change in the active principle of glucocorticoid therapy.

Deflazacort is an intermediate-acting glucocorticoid with potency similar to prednisone, prednisolone, and methylprednisolone. One of its main indications is destined for cases of steroidal tachyphylaxis, i.e. when there is refractoriness to the use of other glucocorticoids. Therefore, it is recognized as a current glucocorticoid, with an equivalent effect to the conventional corticosteroids (JERICÓ; ANDRADE NETO; KOGIKA, 2015; LARSSON e LUCAS, 2016). The use of deflazacort in the described patient achieved therapeutic success considering the permanence of the acceptable number of circulating eosinophils, in addition to the complete regression of clinical signs and intestinal ultrasonographic changes. In dogs, the increased serum alkaline phosphatase activity is usually associated with hepatobiliary disease, osteoclastic activity, usually due to bone neoplasms, and induction by some medications, such as corticosteroids (WIEDMEYER; SOLTER; HOFFMAN, 2002). It has been demonstrated that in 80% of the dogs treated with deflazacort, an amplification was observed in the values of the blood alkaline phosphatase (PEREIRA et al., 2012). However, this increase is reversible in most cases, decreasing after weeks or months when the synthetic steroid is discontinuous (WIEDMEYER; SOLTER; HOFFMAN, 2002). The dose reduction of deflazacort for the present situation was based on the total remission of gastroenteric signs in the clinical and ultrasonographic levels.

Glucocorticoids are highly effective in the management of IHES, but side effects in long-term therapy may lead to impertinent situations and serious damage to animals, such as weight gain, cutaneous atrophy, diabetes mellitus, iatrogenic hyperadrenocorticism, and nephrotoxicity (JERICÓ; ANDRADE NETO; KOGIKA, 2015). For these reasons, the regular and continuous monitoring of animals that are receiving this type of therapy is recommended, so that the undesired effects induced by these drugs are identified and controlled. Such conduct was adopted in the reported animal, which has remained under monitoring even after disease control.

Corticoid therapy may be used in combination with metronidazole. The latter corresponds to an antimicrobial chemotherapeutic classically prescribed in the treatment of infections caused by anaerobic bacteria and protozoa. However, it also acts as a cellular immunomodulator in the gastrointestinal tract (MCTAVISH, 2002). This encouraged the momentary inclusion of this antimicrobial in the therapy of the animal under study.

The preservation of a mild peripheral and medullary eosinophilia, perceived on the 70th day of follow-up of the reported patient, could justify the so-called "physiological eosinophilia", which is a normal characteristic for Rottweiler dogs, according to Neil et al. (2017). Thus, for the specimen in question, although there was no reduction in eosinophil counts (blood and marrow) for the reference interval even with the change in the active principle of glucocorticoid, this condition was accepted as usual for the canid. Although eosinophil values were slightly high, there was no systemic repercussion and there was a steady state of sanity. Some patients with IHES are refractory to glucocorticoids and require treatment with other drugs, such as hydroxyurea, vincristine sulfate, interferon alfa or cyclosporine (AROCH; PERL; MARKOVICS, 2001). For the subject under discussion, to date, the use of these drugs has become unnecessary because of the success of steroidal maintenance therapy.

CONCLUSION

The inclusion of IHES as a differentiation for the causes of eosinophilia in canine species is essential. The recognition of clinical and laboratory manifestations associated with IHES is essential to establish an appropriate diagnosis and therapy. Deflazacort appears as a promising drug for the control of this disease.

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