

Acute Myeloid Leukemia in a Dog Chronically Infected with *Leishmania* spp. and Other Infectious Agents

Leucemia mieloide aguda em cão infectado cronicamente por *Leishmania* spp. e outros agentes infecciosos

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ABSTRACT

Background: Rare studies have described the association of hematopoietic tumors and canine visceral leishmaniasis, however the association between the parasitary disease and neoplasia is still not well established in dogs. Thus, the aim of the present study was to report a case of acute myeloid leukemia (AML) in a dog infected by *Leishmania* spp. and other infectious agents.

Case: A 8-year-old, male Poodle, was brought to the Veterinary Hospital from Universidade Federal Rural do Semi-Árido. The dog had a history of recurrent tick-borne diseases, such as anaplasmosis, over the previous ten months. On physical examination, pale mucosa, enlargement of popliteal lymph nodes, onychogryphosis, purulent nasal discharge, and bilateral blepharitis with purulent discharge were observed. The dog was skinny and infested with ticks. The blood cell count revealed normocytic, normochromic anemia and leukocytosis ($38.000/\text{mm}^3$) with neutrophilia ($30.020/\text{mm}^3$). Serum biochemical tests demonstrated hyperproteinemia due to hyperglobulinemia, hypoalbuminemia, and an albumin:globulin ratio of 0.30. The immunochromathographic test for leishmaniasis was negative. The alterations observed in the bone marrow cytological analysis were suggestive of AML, and *Anaplasma* spp., *Hepatozoon* spp., and amastigote forms of *Leishmania* spp. were observed inside bone marrow cells. After diagnosis, a decision to euthanize the animal was made.

Discussion: Few studies have demonstrated the presence of hematopoietic neoplasia in dogs chronically and simultaneously infected with multiple pathogens. A case of multiple myeloma in a dog associated with infection by *Ehrlichia canis*, *A. phagocytophilum*, *L. infantum*, and *Dirofilaria immitis* is described. Another study reported B-cell lymphoma in a dog with *E. canis* and *Histoplasma capsulatum* infection. The pathogenesis of AML in the reported dog might be associated with continuous antigenic stimulation and chronic inflammation caused by the infectious agents. The pathological changes in bone marrow caused by *Leishmania* are well described, and different combinations of hypoplasia, hyperplasia, or dysplasia of all hematopoietic lineages can occur. The inflammation and chronic stimulation of hematopoiesis can lead to an increased risk of changes in the genetic material of the hematopoietic precursor cells. Thus, there is an increased chance of generation of mutated clones, resulting in hematopoietic malignancies. Immunosuppression is a common condition present in numerous types of neoplasia, especially in those with hematopoietic origins, which increases the vulnerability to opportunistic diseases. In humans, the presence of concomitant neoplasia and leishmaniasis is well documented, However, there are very few veterinary medicine studies on the association between neoplasia and canine visceral leishmaniasis. Cases of hematopoietic tumors, such as multiple myeloma, and multicentric, cutaneous, and cardiac lymphomas, have been described in dogs with leishmaniasis. To the best of our knowledge, this is possibly the first report implicating pathogens of the genera *Leishmania*, *Anaplasma* and *Hepatozoon* as contributors in the etiopathogenesis of AML in the studied animal. Based on all clinical and laboratory findings, we theorize that the prolonged antigenic stimulation and chronic inflammation caused by the infectious agents played a crucial role in the development of leukemia in the dog.

Keywords: myeloproliferative disorder, hemoparasites, canine leishmaniasis.

INTRODUCTION

Canine visceral leishmaniosis (CVL) is an infectious contagious and parasitary chronic disease, caused by the protozoan *Leishmania chagasi* (syn. *L. infantum*), that leads to the manifestation of various unspecific clinical signs, in special viscerocutaneous signs [1]. *Leishmania* amastigote forms parasite cells from mononuclear phagocytic system, which are present in lymphoid organs, such as lymph nodes, spleen, liver and bone marrow [1]. It is known that *L. chagasi* infection triggers a series of bone abnormalities, including dysplastic changes and eritrophagocytosis [5].

Rare studies have described the association of hematopoietic tumors and CVL [3,4,6,10]. It has been suggested that the prolonged antigenic stimulation and chronic immunosuppression in dogs with leishmaniosis can play a crucial role on the etiopathogenesis of hematopoietic malignancies in these animals [5]. However, studies regarding the association of myeloid neoplasia and CVL are very rare. Thus, the aim of this report was to describe a case of acute myeloid leukemia (AML) associated with visceral leishmaniosis and other infectious diseases in a dog.

CASE

A 8-year-old, male Poodle, was brought to the Veterinary Hospital (HOVET) of the Universidade Federal Rural do Semi-Árido (UFERSA). The patient had a history of recurrent thick-borne diseases, such as anaplasmosis, over the previous ten months and had already been treated with doxycycline and other antibiotics, but did not have a favorable therapeutic response.

Pale mucosa, enlargement of popliteal lymph nodes, onychogryphosis, purulent nasal discharge, and bilateral blepharitis with purulent discharge were observed during the physical examination. The dog was skinny and infested with ticks.

Complete blood cell counts, hepatic and renal serum profiles, an immunochromatographic test for the detection of antibodies against *L. chagasi* (Alere Leishmaniose Ac Test Kit)¹, and fine-needle aspiration of bone marrow for cytologic evaluation were all requested.

Normocytic, normochromic anemia was detected (red blood cell count: 3.2 million/mm³; hemoglobin: 7.1 g/dL; hematocrit: 23%; mean corpuscular volume [MCV]: 70 u³; mean corpuscular hemoglobin concentration [MCHC]: 31%). Leukocytosis with

neutrophilia (white blood cell count: 38.000/mm³; neutrophil count: 30.020/mm³) was also observed.

The biochemical abnormalities detected included hyperproteinemia (8.19 g/dL) resulting from hyperglobulinemia (6.29 g/dL), hypoalbuminemia (1.9 g/dL), and an albumin:globulin ratio of 0.30. The result of the immunochromatographic test for leishmaniosis was negative.

The alterations observed in the cytological analysis of the bone marrow were suggestive of AML (Figure 1). Furthermore, *Anaplasma* spp., *Hepatozoon* spp., and amastigote forms of *Leishmania* spp. were observed inside the bone marrow cells (Figure 2). After the diagnosis of CVL associated with AML, a decision was made to euthanize the animal, and necropsy was not authorized.

DISCUSSION

Few studies have demonstrated the presence of hematopoietic neoplasia in dogs chronically and simultaneously infected with multiple pathogens. Geigy *et al.* [6] described a case of multiple myeloma in a dog associated with infection by *Ehrlichia canis*, *A. phagocytophilum*, *L. infantum*, and *Dirofilaria immitis*. Another study reported B-cell lymphoma in a dog with *E. canis* and *Histoplasma capsulatum* infection [2]. In both manuscripts, the authors suggested that the pathogenesis of the tumors might be associated with continuous antigenic stimulation and chronic inflammation caused by the infectious agents. These hypotheses could also be applied to our case, in which the animal was chronically infected with various pathogens when AML developed.

In humans, the presence of concomitant neoplasia and leishmaniosis is well documented. Kopterides *et al.* [8] have established the following four associations between leishmaniosis and cancer: 1) leishmaniosis can mimic a malignant disorder, such as lymphoma; 2) in patients receiving chemotherapy for various malignant disorders, leishmaniosis can present as an infection that is difficult to diagnose and treat; 3) in immunocompromised patients, it is possible to obtain a simultaneous diagnosis of leishmaniosis and a neoplastic disorder in the same tissue samples; 4) *Leishmania* spp. is directly involved in the pathogenesis and development of malignant lesions, an association which we considered as a hypothesis in our case [8].

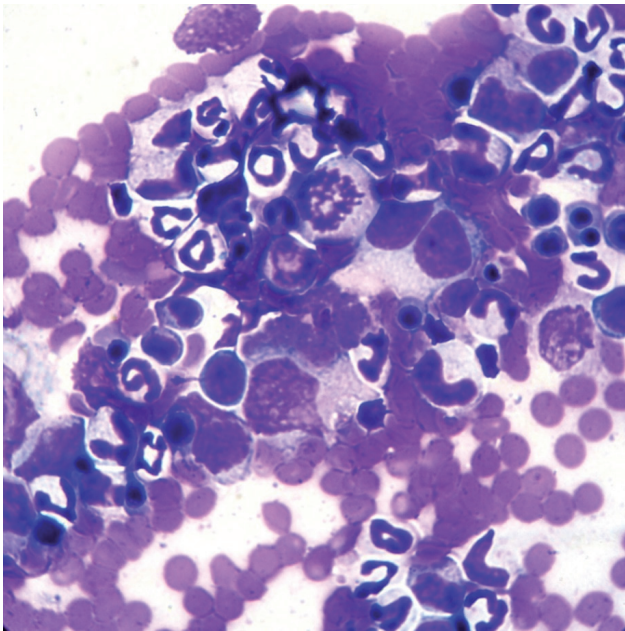


Figure 1. Bone marrow cytological photomicrograph showing blastic cells with malignancy criteria, such as mitosis figures and maturative asynchronism (Diff-Quick staining, 100x magnification).

Due to the high prevalence of CVL in endemic areas, the coexistence of these conditions might be a coincidence. However, there are very few veterinary medicine studies on the association between neoplasia and CVL. Cases of hematopoietic tumors, such as multiple myeloma, and multicentric, cutaneous, and cardiac lymphomas, have been described in dogs with leishmaniasis [3,4,6,10]. To the best of our knowledge, this is possibly the first report implicating pathogens of the genera *Leishmania*, *Anaplasma* and *Hepatozoon* as contributors in the etiopathogenesis of AML in the studied animal. This association was made based on the fact that some blood parasites, such as *Leishmania* spp., target organs rich in cells of the mononuclear phagocytic system, such as lymph nodes and bone marrow, causing a series of injuries. The chronic antigenic stimulation may contribute to neoplastic transformation resulting in AML. The pathological changes in bone marrow caused by *Leishmania* are well described, and different combinations of hypoplasia, hyperplasia, or dysplasia of all hematopoietic lineages can occur [5].

The inflammation and chronic stimulation of hematopoiesis can lead to an increased risk of changes in the genetic material of the hematopoietic precursor cells. Thus, there is an increased chance of generation of mutated clones, resulting in hematopoietic malignancies [7]. This citation reinforced our hypothesis that the hemoparasites exerted an important role in the development of AML in the dog in our study.

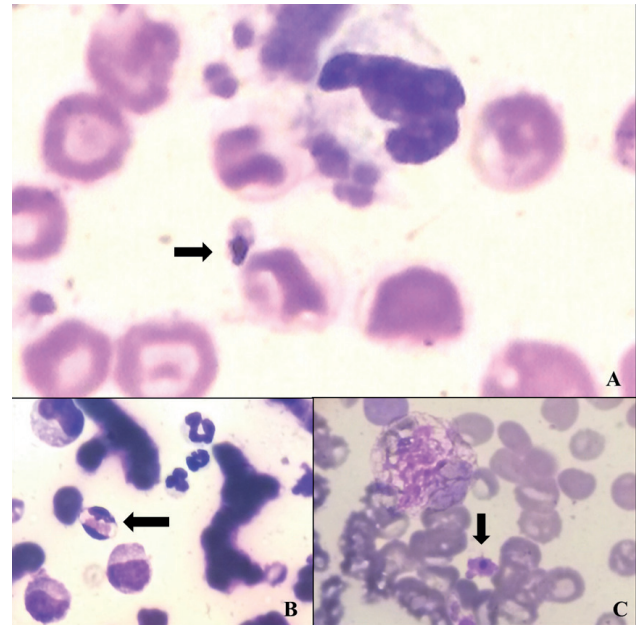


Figure 2. Hemoparasites observed on bone marrow cytological examination. A- *Leishmania* spp. (arrow); B- *Hepatozoon* spp. (arrow); C- *Anaplasma* spp. (arrow) [Diff-Quick staining, 100x magnification].

In the current study, a diagnosis of CVL was obtained only by direct parasitological examination, using fine-needle aspiration of the bone marrow, despite negative serology for leishmaniasis. Although the serological methods present a satisfactory sensitivity and specificity, failure can occur in some situations - for example, when the animal is in the prepatent period, since the average time for seroconversion is five months. There are individuals that will never seroconvert; some animals are seropositive and convert to seronegative, but remain infected [1,9]. With regard to the dog reported in our study, we hypothesize that due to the chronicity of the infection, the dog became anergic, ceasing production of antibodies against *Leishmania*; however, it was still infected by the protozoan. Hence, the serological test result was negative.

Immunosuppression is a common condition present in numerous types of neoplasia, especially in those with hematopoietic origins, which increases the vulnerability to opportunistic diseases [11]. For this reason, it is of fundamental importance that the presence of CVL and other hemoparasites be investigated in dogs affected by oncologic diseases, since coinfections represent a complicating factor in the treatment of the animal. Most oncological therapeutics also predispose the patient to immunosuppression, further deteriorating the general health of the animal when infectious diseases are acquired. Thus, the prevention of such disorders is mandatory during antineoplastic treatment, especially in areas in which CVL is endemic.

Further studies are still necessary to investigate and elucidate the influence of microorganisms of the genera *Leishmania*, *Anaplasma*, and *Hepatozoon* on the genesis of some neoplasms. We strongly believe that these pathogens played an important role in the development of AML in the reported dog.

MANUFACTURER

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Declaration of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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