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Case Report - Veterinary Medicine

Monoclonal gammopathy leading to blood hyperviscosity syndrome in a dog – case report

[*Gamopatia monoclonal com síndrome da hiperviscosidade sanguínea em cão – relato de caso*]

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ABSTRACT

Monoclonal gammopathy (MG) is rare in dogs and multiple myeloma (MM) is its main cause. This study reports the case of a female dog which presented MG associated with a MM and consequent blood hyperviscosity syndrome (HVS). Patient presented systemic hypertension, renal disease, chorioretinitis and secondary glaucoma due to HVS. Serological tests for leishmaniasis and for ehrlichiosis demonstrated negative and score 4 from 5, respectively. Non-regenerative anemia, thrombocytopenia, hyperproteinemia, hypoalbuminemia, hyperglobulinemia, creatinine and blood urea nitrogen (BUN) increases, hypercalcemia, hyperphosphatemia, proteinuria, decreased urinary density, and monoclonal peak of gamma globulins were observed. First myelogram identified 81% of medullary plasmacytosis which suggested MM. Plasmapheresis and chemotherapy with melphalan and prednisolone were performed with positive results. The treatment was effective with complete remission of HVS signs, medullary plasmocytosis reduction (21,8%) and malignant criteria decrease, as well as neoplastic control.

Keywords: chemotherapy, gamma globulins, medullary plasmocytosis, myeloma, neoplasia

RESUMO

Gamopatia monoclonal (GM) é rara nos cães, e o mieloma múltiplo (MM) é a sua principal causa. Este estudo descreve o caso de uma cadela que apresentou GM associada ao MM e consequente síndrome da hiperviscosidade sanguínea (SHS). A paciente apresentou hipertensão arterial sistêmica, doença renal, coriorretinite e glaucoma secundário decorrentes da SHS. Testes sorológicos para leishmaniose e para erliquiose apresentaram baixos títulos e escore 4 e 5, respectivamente. Anemia arregenerativa, trombocitopenia, hiperproteinemia com hipoalbuminemia e hiperglobulinemia, aumentos de ureia e creatinina, hipercalcemia, hiperfosfatemia, proteinúria, diminuição da densidade urinária e pico monoclonal de gamaglobulinas foram identificados. Foi consignado um primeiro mielograma, com identificação de 81% de plasmocitose medular, sugestivo de MM. Dessa forma, foi instituída plasmaférese e quimioterapia com melfalano e prednisolona, com resultados positivos. O tratamento instituído foi efetivo, com auxílio na completa redução dos sinais da SHS, na diminuição da plasmocitose medular (21,8%) e dos critérios de malignidade, bem como no controle da neoplasia.

Palavras-chave: gamaglobulinas, leishmaniose, mieloma, plasmocitose medular, quimioterapia

INTRODUCTION

Monoclonal gammopathy (MG) is a rare alteration in the serum globulins and is characterized by a monoclonal peak in the beta or gamma fractions on the protein electrophoresis graphic. It is generally caused by multiple myeloma (MM), Waldenström's macroglobulinemia, chronic lymphocytic leukemia, plasmocytic leukemia, amyloidosis and, rarely, chronic pyoderma, ehrlichiosis and leishmaniasis (LCan) (Antognoni *et al*., 2010).

MM is a malignant neoplasia characterized by plasma cells proliferation or by their precursors in the bone marrow which leads to a systemic involvement with excessive production of immunoglobulins, also known as M component

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or monoclonal proteins (Wyatt *et al*., 2019). MM is the main cause of MG in dogs and its diagnosis includes detection of medullary plasmacytosis in myelogram; monoclonal peak of proteins in urine or plasma electrophoresis; detection of Bence Jones protein in urinalysis; and detection of osteolytic lesions in x-ray exams (Fernández and Chon, 2018; Moore and Avery, 2019). Therefore, other concomitant diseases than MM must be excluded, such as LCan and ehrlichiosis (Ferreira *et al*., 2013).

In human medicine, identification of major and minor criteria for MM diagnosis are described. Major criteria include detections of neoplastic plasma cells in the bone marrow; bone marrow plasmacytosis greater than 30%; and a monoclonal immunoglobulin peak. Minor criteria include findings of medullary plasmacytosis between 10 and 30%; osteolytic lesions and monoclonal peak lower than the value referred for the major criteria (Geigy *et al*., 2013).

Hyperviscosity syndrome (HVS) occurs due to either elevation of the blood cellular or acellular fractions. However, the term HVS is best reserved for an increase in serum proteins which leads to a state of emergency for the dogs (Adams *et al*., 2009).

This report aimed to describe a case of a mixed breed female spayed dog which presented MG due to MM leading to HVS.

CASE REPORT

A 10-year-old, mixed breed, spayed female dog attended a veterinarian appointment. The animal's previous history included exams whose results revealed pancytopenia and creatinine increase; score 4 from 5 for ehrlichiosis serology; negative serologies (enzyme-linked immunosorbent assay [ELISA] and indirect immunofluorescence) for LCan; and hepatosplenomegaly on ultrasound. In addition, patient was previously treated with doxycycline and prednisolone for ehrlichiosis; imidocarb dipropionate and thymomodulin, with no improvement in clinical signs.

On anamnesis, the owner described that the animal had been presenting apathy, hyporexia, exercise intolerance, polyuria and polydipsia. On physical exam, severe apathy, body score 4 from 9, pale mucous membranes and dehydration estimated at 6% were noted. Ophthalmic evaluation revealed chorioretinitis on the right eye and secondary glaucoma on the left eye.

Hemogram, serum biochemistry and urinalysis revealed anemia, reticulocytosis, thrombocytopenia, leukopenia, neutropenia and lymphopenia, increased creatinine and blood urea nitrogen (BUN), hypercalcemia, hyperproteinemia, hypoalbuminemia, hyperglobulinemia (18,4g/dL), low urinary density, and proteinuria. Serum protein electrophoresis was also performed which results revealed a monoclonal immunoglobulin peak (Figure 1).

The patient also presented HVS severe signs such as: increased intraocular pressure (IP) in the left eye, systemic hypertension, and biochemical tests indicated increase immune globulins (18,4g/dL). Subsequently, plasmapheresis was performed with autologous erythrocyte concentrate after normovolemic dilution and washing of red blood cells. For that procedure, 40mL of whole blood was collected through the patient's external jugular vein, and then 10mL of erythrocyte concentrate was diluted in 30mL of 0.9% sodium chloride.

By the end of the plasmapheresis, venipuncture for blood sample was collected through the patient's external jugular for gamma globulins pre-plasmapheresis and pos-plasmapheresis measurements. Results revealed globulins decrease values, from 18,4g/dL to 16,4g/dL.

Echocardiogram revealed mild mitral valve insufficiency without hemodynamic repercussions and type 1 diastolic dysfunction. Chest (right lateral, left lateral and dorsoventral incidences), pelvis (right lateral, left lateral and ventrodorsal) and skull (laterolateral, rostroventral and oblique) x-rays were taken, and no areas of osteolytic lesions were observed. Electrocardiogram showed sinus arrhythmia and suggested left atrial and ventricular overload.

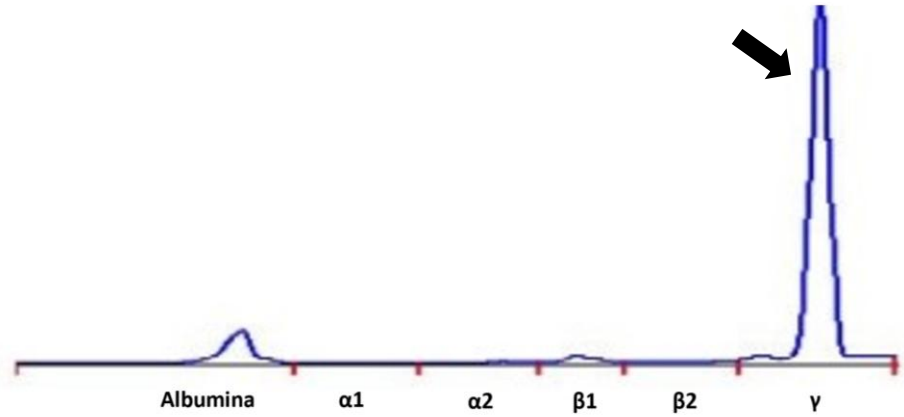

Figure 1. Graphic representation of a mixed breed female dog's serum protein electrophoresis. Results show a monoclonal gamma globulin peak of γ-globulins (black arrow) related to a multiple myeloma (MM).

Bone marrow aspirate (BMA) was performed and revealed in cytological evaluation hypercellular sample with a reduced percentage of fat (< 25%), as well as dense monomorphic population composed predominantly of plasma cells (81%); those cells exhibited mild to moderate anisocytosis and anisokaryosis, coarse chromatin, frequent bi, multinucleations and "flame cells". Megakaryocytic series was slightly reduced. Erythroid and myeloid series were significantly reduced and were predominantly composed of mature cells. In addition to these lineages, lymphocytes (7.6%) and rare macrophages (0.4%) were observed. Those findings were compatible with marked erythroid and myeloid hypoplasia and mild megakaryocytic hypoplasia, as well as plasmocytic neoplasia, suggesting MM (Figure 2).

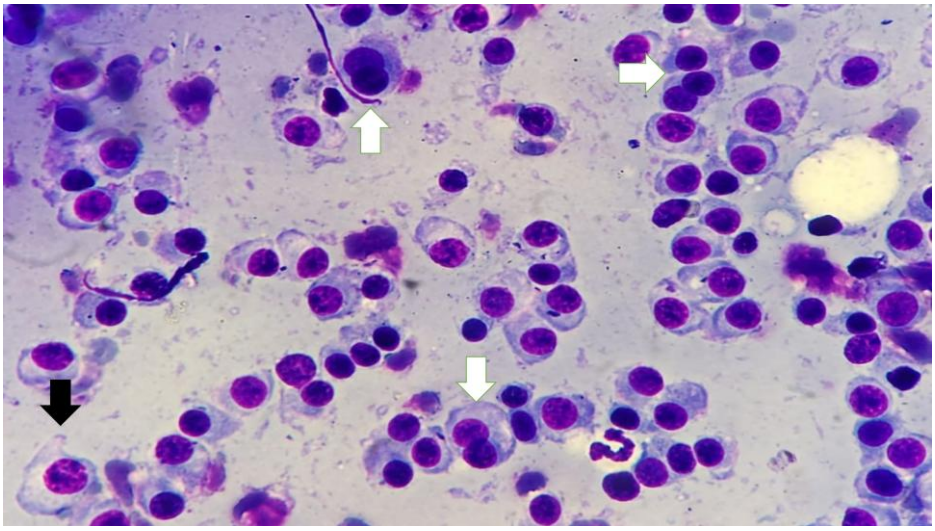

Figure 2. Photograph of a mixed breed dog bone marrow aspiration slide. Note: anisocytosis (different cells sizes), anisokaryosis (different nucleoli sizes), multinucleated plasma cells (white arrows) and flame cells (black arrow). Those findings suggest multiple myeloma (MM). Diff-Quik staining. 1000x.

Melphalan (0.1mg/kg/SID for 10 days and then 0.05mg/kg/SID for undetermined period) and prednisolone (1mg/kg/SID for 10 days and then 0.5mg/kg/SID/VO also for undetermined period) were chosen as chemotherapy treatment. Ophthalmic therapy prescription was based on prednisolone acetate eye drops (1 drop in each eye, TID, until further recommendations),

dorzolamide (1 drop in the left eye, QID), lubricating eye drops based on 0.4% hyaluronic acid (1 drop in each eye, BID, until further recommendations).

Eight days later, the patient returned to a follow-up and to start chemotherapy. On physical examination, central ulceration and absence of pupillary and threat reflexes were observed as ophthalmic conditions. Thus, enucleation of the left eye was decided as the most adequate therapy.

Three months later, animal's owner reported the patient's clinical signs improvement, with weight gain and increased disposition for physical activities. A second bone marrow aspirate through sternum was conducted and results demonstrated decrease myeloid: erythroid ratio and medullary plasmacytosis (21.8%).

DISCUSSION

On this report, MG and SHS clinical signs observed were highly possible due to MM. On the other hand, some authors report that infectious diseases, such as LCan and canine ehrlichiosis, may also lead to immune globulins monoclonal peaks, although in a rare form. This information emphasizes the importance of investigation of concomitant infectious diseases (Ferreira *et al*., 2013).

The diagnosis of MM was made by medullary plasmacytosis and by the presence of 81% of atypical plasma cells in myelogram. It was also noted anisocytosis, anisokaryosis, mitotic figures, and detection of a monoclonal peak of gamma globulins (10.28g/dL). Those results are described as only major criteria in human medicine diagnosis classification for MM.

Authors describe that MM diagnosis is made by identification of at least two of the following items: recognition of plasma cell infiltration in the bone marrow; identification of MG in urine or plasma electrophoresis; detection of Bence Jones protein in urine; and x-ray exams noticing osteolytic lesions (Fernández and Chon, 2018; Moore and Avery, 2019; Moore *et al*., 2021).

Serologies for leishmaniasis and for ehrlichiosis were performed and results had shown high titers only for canine ehrlichiosis. Therefore, the recommended treatment with doxycycline for 4 weeks was accomplished (Sainz *et al*., 2015) without any improvement in the patient clinical signs, as well as a worsening on thrombocytopenia and neutropenia noticed in hemogram.

The patient of this report probably had another important concomitant disease rather than the ehrlichiosis that had not been diagnosed at that time. However, no new serology for ehrlichiosis was performed when treatment with doxycycline was finished and no new serum electrophoresis was made due to the owner's financial restriction. Plus, circumstances may not exclude the possibility of ehrlichiosis has had a connection with the MG detected, even if ehrlichiosis is a rare cause for MG. Furthermore, there is also the possibility of the chronic infection and inflammation caused by *Ehrlichia* sp. having been a carcinogenic event for the development of MM.

Clinical signs presented were non-specific, as well as those described for MM whose clinical manifestations depend on the anatomical location of neoplastic cells infiltration and on the monoclonal proteins' deposition area (Caldin *et al*., 2019; Muñoz *et al*., 2013; Wyatt *et al*., 2019).

Hemogram, serum biochemistry and urinalysis results were similar to those described by Muñoz *et al*. (2013) for dogs that presented MM. Non-regenerative anemia, thrombocytopenia, hyperproteinemia, hypoalbuminemia, hyperglobulinemia, creatinine and BUN increases, and hypercalcemia improvements after started chemotherapy were observed. That result enhances the patient's good response to the chosen therapy protocol.

Creatinine and BUN increases in the blood as well as urinalysis alterations may have been caused by reduced renal perfusion due to SHS (prerenal azotemia) associated with monoclonal proteins nephrotoxicity, hypercalcemia, hypertension, dehydration, and use of nephrotoxic drugs (Fernández and Chon, 2018).

Hypercalcemia and hyperphosphatemia may have been established by the secretion of a protein like parathyroid hormone by neoplastic

cells and/or nephropathy, with secondary renal hyperparathyroidism development. However, no areas of osteolysis were observed on the patient's x-ray images. Furthermore, hypercalcemia may have contributed to the development of polyuria and polydipsia, since this alteration may lead to nephrogenic *diabetes insipidus* and decreases renal concentration capacity leading to urinary density reduction (Geigy *et al*., 2013; Rafae *et al*., 2018).

HVS severity depends on the type of M component involved and it is more intense in IgM-macroglobulinemia due to its high molecular weight. Consequently, animals may present hemorrhagic diathesis, disorientation, convulsions, behavioral changes, congestive heart failure, renal failure, and ophthalmopathies (Kristal, 2020; Santana *et al*., 2016). HVS clinical signs described previously for other authors were compatible with the clinical signs, alterations on the physical exams, and laboratory findings presented by the patient. Increased IP, systemic hypertension, intense apathy, and kidney disease (HVS classic signs) were the main findings which characterized as an emergency condition for the patient.

Immunofixation is necessary for the immunoglobulin subclass evaluation. However, that exam was not performed due to the owner's financial restriction and to the unavailability of the exam in Brazil (Moore and Avery, 2019). Therefore, the immunoglobulin M involvement which characterizes Waldenström's macroglobulinemia may not be excluded.

Plasmapheresis was performed as part of the emergency therapy. Later in the procedure, a decrease in globulins measurement from 18.4 g/dL to 16.4 g/dL was noticed. That decrease emphasizes the plasmapheresis procedure importance and effectiveness to reduce SHS signs and its consequences to the animals (Lippi *et al*., 2015; Santana *et al*., 2016).

Chemotherapy using melphalan with prednisolone is recommended for MM treatment (Kristal, 2020; Santana *et al*., 2016). According to Fernández and Chon (2018), dogs that received this protocol daily had an average survival time of 540 days and a response rate of 92%. The same was observed in this report, with the patient's good response to the chemotherapy, important reduction in medullary plasmacytosis and in malignancies criteria, as well as the patient clinical signs improvement.

CONCLUSIONS

MM is the main cause of MG in dogs. However, the possibility of concomitant chronic inflammation and infectious diseases must be excluded. In this report, a patient presented GM due to MM. Chemotherapy protocol with melphalan and prednisolone has shown as a good option for the treatment of MM, with dog's clinical signs complete remission, medullary plasmacytosis and malignant criteria decreases, as well as neoplastic control.

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