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Case Report

Multiple myeloma in a dog

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Abstract

Multiple myeloma is an uncommon malignant neoplastic disease of humans and domestic animals associated with the excessive production of immunoglobulin by proliferated plasma cells. This article describes the findings associated with this disease entity in a 12-yr-old female Boxer dog. Clinically, the dog was very thin and had polyuria, polydypsia, and motor incoordination. Laboratory examinations revealed hypergammaglobulinemia, hypercalcemia, leucopenia, anemia, and thrombocytopenia. Radiographical evidences of osteolytic bone lesions were observed in various regions of the vertebrate column. Multiple myeloma was initially diagnosed by cytology from a fine needle bone marrow aspirate. Gross lesions suggestive of multiple myeloma were observed in the marrow of long bones, with associated widespread lymph node enlargement, splenomegaly, and hepatomegaly. Histopathology confirmed multiple myeloma in the bone marrow with metastases to the liver, lymph nodes, and spleen.

Key words: dog; multiple myeloma; hypergammaglobulinemia; pathology.

Multiple myeloma (MM) is a rare malignant tumor of plasma cells that is associated with excessive secretion of immunoglobulin (4, 3). Cases of this tumor have been described in several species of domestic animals (4) and humans (2). Dogs are more frequently affected than other domestic animals (3); but there is no apparent breed predisposition, and the tumor accounts for only 1% of all neoplastic lesions (4).

Although the etiology of MM in domestic animals has not been fully elucidated, the participation of genetic predisposition, viral infections, chronic antigenic stimulation, and the exposure to environmental carcinogens (4) have been associated with this tumor. The salient laboratory finding of MM is hyperglobulinemia due to increased production of immunoglobulin (Ig) or subunits of Ig by neoplastic plasma cells (3, 10). While characteristic pathological alterations (such as osteolytic bone lesions, hypercalcemia, renal disease, hemorrhage, immunodeficiency, and cardiac abnormalities) of MM are due to neoplastic proliferation of B cells in the bone marrow and other tissues (4). In humans, this disease is associated with osteolytic lesions, anemia, renal insufficiency, and recurrent bacterial infections (2). Only one published report from Brazil was located in domestic animals (1); however, the article described the evolution and treatment of MM in a dog with neurological complications. This report is important since it describes the clinical, laboratorial, radiological, and pathological findings associated with this tumor in a dog; the pathogeneses associated with these lesions are also

discussed.

In mid-July 2006, a 12-year-old, spayed, female Boxer dog was admitted at the Veterinary Teaching Hospital, Universidade Estadual de Londrina, Paraná, Southern Brazil, with a chronic history of ataxia and exhaustion during 4 months. Locomotory impairment was progressive, and the bitch was unable to remain standing during clinical evaluation. Clinical examination on admission revealed that the animal was very thin, attentive to movement, and with congested mucous membranes. Additionally, polyuria, polydypsia, motor incoordination, and normal body temperature without signs of apparent organomegaly but with sensitivity to caudal abdominal palpation were observed. Simple radiography of the spinal column revealed multiple osteolytic lesions of the scapulas, long bones, and of the cervical, thoracic, and lumbar vertebrates (Fig. 1A-B). Clinical and radiological evaluations were done; while serological analysis (to detect hypergammaglobulinemia) and a fine needle aspirate of bone marrow were performed. At this moment, differential clinical diagnosis included multiple myeloma, canine ehrlichiosis, and leishmaniosis. The animal was hospitalized and monitored for nine days (until 29, July). A chemotherapy protocol based on melphalan (0.1 mg/kg) and prednisone (0.5 mg/kg) was implemented 14 days (on 3rd, August) after a diagnosis of multiple myeloma was established by cytology of bone marrow and radiographic findings, and then confirmed by protein analysis. The dog was evaluated for hematological and biochemical abnormalities for seven weeks post-diagnosis. However, the corporal condition deteriorated and the animal was euthanized. Necropsy was preformed soon after death; selected tissues were fixed in 10% buffered formalin solution and routinely processed for histopathological evaluation.

Serum protein electrophoresis revealed hypergammaglobulinemia with a monoclonal spike (7.21 g/dL; normal 0.06 – 0.14 g/dL; Fig. 1C). Marked leucogram abnormalities were observed at admission and included: leucopenia (neutropenia and lymphopenia) with thrombocytopenia, but were not maintained constant throughout the course of treatment. However, reduced red blood cell values (hematocrit and hemoglobin) were observed during most of the period, while thrombocytopenia occurred only during the first week after a diagnosis of MM was established. Serum calcium levels were elevated (13.6 mg/dl; normal 9-11.3 mg/dl) at the onset of the disease and subsequently reduced. Microcytic normochronic anemia and normocytic normochromic anemia were also observed. There was marked elevation in serum creatinine (3.3 mg/dL; normal 0.5-1.5 mg/dL) and urea (93.6 mg/dL; normal 10-24 mg/dL) values; these were only monitored during the first week after diagnosis. Additionally, urine analysis, realized on admission by dipstick evaluation, demonstrated discrete proteinuria, severe hematuria and bacteruria, in addition to isosthenuria (specific gravity 1015).

Cytology of the fine needle aspirate of the bone marrow obtained from the iliac crest revealed proliferation of plasma cells that demonstrated discrete anisocaryosis with rare mitotic figures and contributed to 13% of all nucleated cells; hyperplasia of granulocytic series, hypoplasia of the erythrocytic series, and normoplasia of megakaryocytic series were also observed; the myeloid:erythroid ratio was 4.15:1.

At necropsy, there was moderate dehydration with significant alterations to the marrow of the long bones and organs of the abdominal cavity. Foci of opaque, gelatinous and irregularly shaped tumorous masses were observed admixed in the normal marrow of the long bones (Figure 1D). The spleen demonstrated several, different-sized (0.2 – 3 cm diameter), whitish-grey, firm, elevated nodules that were randomly distributed throughout the splenic parenchyma (Figure 1E). The iliac lymph nodes were severely hypertrophic and coalescing, and formed a huge abdominal mass (2.5 x 7.5 cm) caudal to the kidneys; sectioned surface revealed various whitish-grey to hemorrhagic, firm and well defined nodular areas (Figure 1F). Other significant gross lesions included two nodular whitish-grey masses (3 cm diameter) adhered to the mesenteric tissue; severe enlargement of superficial and internal lymph nodes, and discrete hepatomegaly.

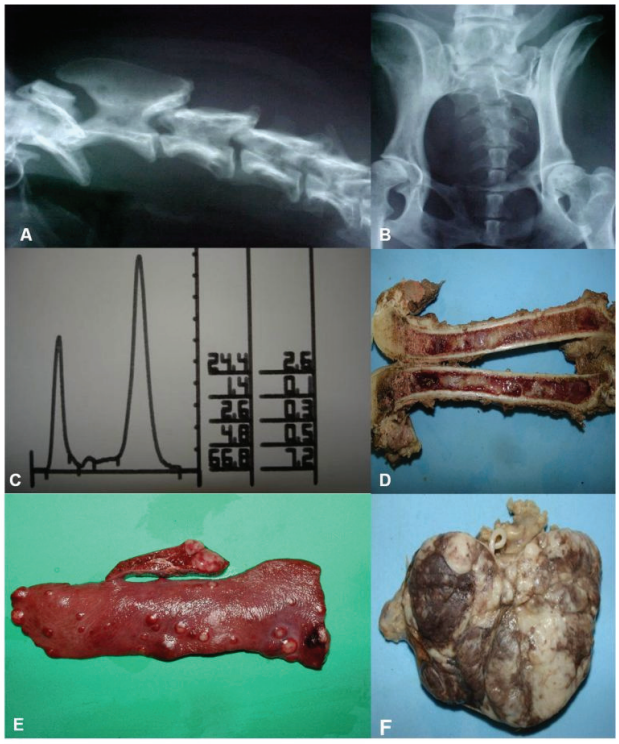

Figure 1 - Boxer dog; gross manifestations of multiple myeloma. Observe severe multifocal osteolytic lesions affecting all cervical vertebrates (A) and the hip joint, proximal extremity of the femur, wing of the ileum, and the 7th lumbar vertebrate (B). Protein electrophoresis; there is hypergammaglobulinemia with a monoclonal spike (C). There are several foci of whitish gelatinous tumorous masses within the bone morrow (D). Spleen, there are several different-sized tumorous nodules distributed throughout the surface and parenchyma of the organ (E). Fused lymph nodes removed from the abdominal cavity; observe marked lost of cortical and medullar differentiation (F).

Histological evaluation of the bone marrow

revealed severe proliferation of neoplastic plasma cells, forming a compact pattern, which resulted in substitution of normal hematopoeitic tissue (Figure 2A). Metastases of the primary tumor were observed in the spleen, lymph nodes, mesenteric nodules, and liver (Figure 2B-D). Significant non-neoplastic lesions were observed in the kidneys, being characterized by severe, multifocal membranoproliferative glomerulonephritis, discrete foci of metastatic mineralization of basement membranes of renal tubules, and multifocal, discrete interstitial fibrosis; significant diagnostic alterations were not observed in the other tissues examined.

An initial diagnosis of multiple myeloma (MM) was made by cytological evaluation of the bone marrow aspirate and characteristic radiological evidences, and later reinforced by serum monoclonal gammopathy and histological findings; these observations are diagnostic for MM (3, 4, 10). Although a diagnosis of MM can be also confirmed by light chain proteinuria, the so-called Bence-Jones proteins (4, 10); this analysis was not done in this cases, since the results of the other diagnostic parameters utilized were sufficient to characterize this lesion. Further, simple routine cytological evaluation of bone marrow aspirate with more than 5-30% of plasma cells is considered diagnostic for multiple myeloma (6, 10); in this case, the plasma cell population contributed to 13% of all nucleated cells observed in the bone marrow.

It must be highlighted that the isolated finding of monoclonal gammopathy is not diagnostic for MM, since this abnormality may also occur in other tumors (lymphoma, acute and chronic lymphocytic leukemia) and

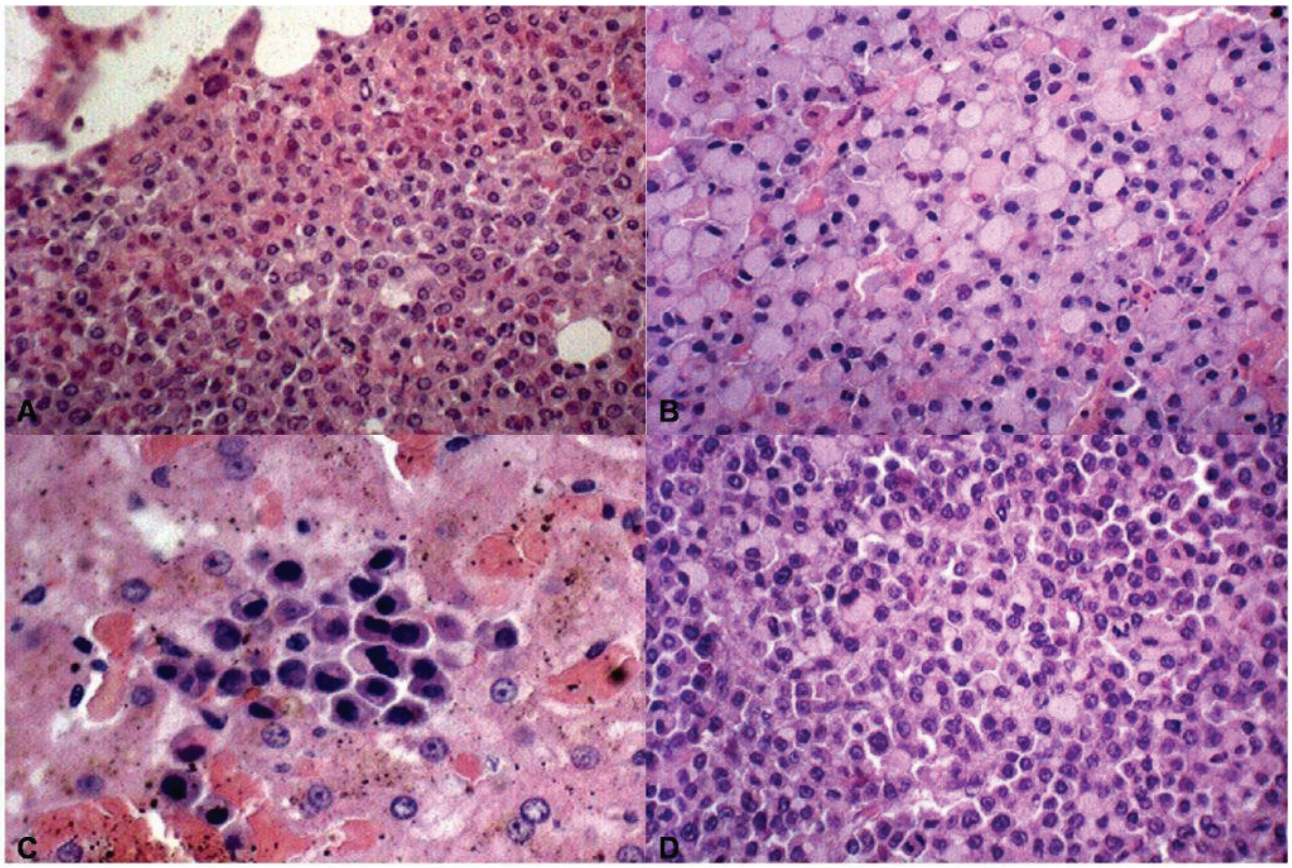

Figure 2 - Boxer dog; photomicrography of plasma cell tumor. There is severe and diffused proliferation of plasma cells resulting in substitution of the normal architecture of the marrow of long bone (A). Observe metastases of the tumor to the mesenteric tissue (B), liver (C), and lymph node (D). (HE, Ob. 40x).

in chronic infectious canine diseases such as ehrlichiosis and leishmaniosis (9, 10). However, in these diseases, the M protein normally demonstrates stable and moderate concentrations, and there is no formation of the Bence-Jones proteins, osteolysis or cytopenia (4).

Multiple myeloma was diagnosed in the bone marrow with metastases to the spleen, lymph nodes, and liver of this dog; these organs represent the most common sites of tumor dissemination (4). The involvement of various tissues/organs in this disease has been related to the proliferation of a clone of B lymphocytes that may differentiate into abnormal plasma cells (8). This clone produces what is referred to as paraprotein (also known as M protein or monoclonal gammopathy) that may be a whole immunoglobulin molecule of any group of a heavy or light chain (4,10); further, this animal demonstrated a

monoclonal spike of hypergammaglobulinemia that is characteristic of this disease. Thus, the presence of this protein, detectable by serum electrophoresis, associated with cytology aspirate of bone marrow with characteristic findings is diagnostic for MM. However, in rare cases of MM there are no detection of monoclonal protein during serum or urine electrophoresis (5); these are classified as nonsecretory multiple myelomas (10).

This dog demonstrated osteolytic lesions in the cervical, thoracic, and lumbar vertebrates, and at the extremities of the femur; these alterations explain the incapacity of the animal to remain standing for long periods during clinical examination. Lameness, as occurred in this case, diffused osteopenia and pathological fractures of long bones are the most common clinical manifestations of MM in affected dogs (4, 10), and more than 33% of dogs with MM may also have radiographic evidence of osteoporosis (10). In humans, the pathogenesis of myeloma bone lesions have not been fully elucidated, but recent studies have indicated that the molecular interaction of stromal and neoplastic plasma cells is associated with bone destruction (7).

This dog also demonstrated transient anemia during the disease process; anemia is a common manifestation of this disease in humans (2), but not frequently observed in affected domestic animals. Anemia in dogs with MM has been associated with blood loss due to platelet destruction, presence of concomitant chronic disease, and accelerated destruction of erythrocytes (8); all of these alterations were observed in this case. The leucopenia and thrombocytopenia herein described occur in more than 33% of animals with MM and have been related to the substitution of normal bone marrow by neoplastic plasma cells (10), which then correspond to the glossy-like appearance of the bone marrow of this dog.

The renal dysfunction observed by serum and urine analyses and confirmed by histopathology in this case, is another frequent clinical complication of MM and may occur in 33-50% of dogs with this disease (10); further, the glomerular lesions herein described have been related to the deposition of the Bence-Jones proteins (4). Additionally, renal insufficiency in MM has been associated with tumor dissemination into renal parenchyma, hypercalcemia, amyloidiosis, dehydration, and reduced perfusion due to the hyperviscosity syndrome (10). This dog also demonstrated hypercalcemia by serum analysis and histopathology; 15-20% of affected dogs with MM may also have concomitant elevations of serum calcium levels (10). Hypercalcemia in MM has been related primarily to the production of osteoclast stimulating substances by neoplastic plasma cells (4, 10), or may be associated with concomitant renal disease (10).

In conclusion, multiple myeloma was diagnosed and confirmed in this dog due to the characteristic radiological, laboratorial, cytological, and histopathological findings that are consistent with this disease. This is an uncommon malignant plasma cell tumor that is associated with the excessive secretion of immunoglobulin. This report contains information that would be useful to assist pathologist and veterinarians in the diagnosis and understanding of this remarkable disease entity in dogs.

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