

## Canine Multiple Myeloma

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### Introduction

Multiple myeloma or plasma cell myeloma, is a neoplasm of well-differentiated B cell lymphocytes typically originating from the bone marrow. Neoplastic cells can metastasize widely, having a predilection for bone and resulting in osteolysis. The malignant transformation of a single B cell can secrete a homogenous immunoglobulin product known as paraprotein, which will mimic the structure of normal immunoglobulins. Overabundant production of paraprotein, consisting of any of the immunoglobulin classes, will appear as a sharp, well-defined peak or monoclonal gammopathy on serum electrophoresis.

The most frequently encountered multiple myelomas secrete IgG or IgA paraproteins, however IgM myelomas (macroglobulinemia) have also been diagnosed in companion animals. Light chain disease is caused by plasma cell overproduction of the light chain segment of the immunoglobulin complex, consisting of either the lambda or kappa light chain. These proteins are referred to as Bence-Jones proteins and are the most commonly observed immunoglobulin fragments in the monoclonal gammopathies.<sup>2</sup> There are rare instances where a malignant plasma cell neoplasm will be nonsecretory. These tumors occur in approximately 1% of all cases of multiple myeloma and are referred to as nonsecretory multiple myeloma. In this type of neoplasm, malignant plasma cells produce either fragments or intact monoclonal immunoglobulins but do not secrete them from the cell. In rare cases of nonsecretory multiple myeloma, recognizable immunoglobulins are not produced.<sup>8</sup>

### Incidence and Predisposition

Multiple myelomas have been described most commonly in dogs, humans, and cats, but also have been diagnosed in mice, horses, cows, pigs,

ferrets, and rabbits.<sup>10</sup> They account for < 1% of all malignant canine tumors, ~ 8% of all malignant hematopoietic tumors in dogs, and 3.6% of all primary and secondary bone tumors diagnosed by biopsy.<sup>8,9,10</sup> There is no current evidence suggesting any age, sex or breed predilection. However genetics, viral infections, chronic immune stimulation, and exposure to carcinogens have been identified as possible contributing factors.<sup>9,10</sup>

### **Clinical Presentation**

The clinical manifestations of multiple myeloma are highly variable and may affect multiple organ systems. The presentation of a patient with multiple myeloma will depend on the type of neoplastic cell, type of immunoglobulin produced, location of the tumor, and severity of growth and infiltration. Affected dogs can exhibit signs of lethargy, weakness, lameness, bone pain, hemorrhage (e.g, petechiae on mucous membranes, gingival bleeding, and epistaxis), polyuria / polydypsia, and/or neurologic deficits.<sup>11</sup> Other presenting signs of disease may include hypertension, ophthalmic abnormalities (e.g., venous dialation with sacculation, retinal hemorrhages, and retinal detachment), neurologic dysfunction (including seizures), organomegaly, and suggestion of multiple organ failure.<sup>9</sup>

Clinical signs and symptoms may be present for up to 1 year before a definitive diagnosis of multiple myeloma is made. Patients can also present with recurrent infections, non-regenerative anemia, pathologic bone fractures, and/or seizures. Complications secondary to multiple myeloma may include renal failure, infections secondary to immunosuppression, clotting disorders, chronic anemia, cardiac insufficiency, and neurologic dysfunctions such as senility.

### **Diagnosis**

Diagnosis of multiple myeloma in dogs requires at least two of the following criteria:<sup>5</sup>

- 1.) Radiographic evidence of osteolysis
- 2.) >20% plasma cells in bone marrow aspiration or biopsies
- 3.) Monoclonal gammopathy on serum protein electrophoresis
- 4.) Bence-Jones proteinuria

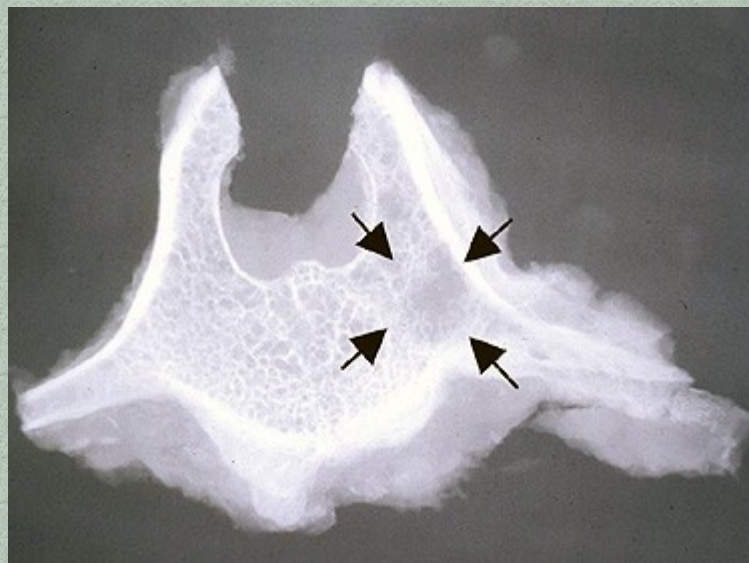
### **Radiographic Evidence of Osteolysis**

Multifocal radiolucent lesions within the bone may be seen in ~ 40% of dogs suffering from multiple myeloma (in contrast, osteolytic lesions rarely are seen in cats).<sup>12</sup> The bones most commonly involved in canine multiple myeloma include the spine, pelvis, ribs, skull, and proximal extremities.<sup>9</sup> Malignant plasma cell tumors present in the bone marrow are often osteolytic. The presence of these tumors directly induces bone resorption by production of osteoclastic-activating factor from neoplastic



cells. Osteolysis is also induced secondary to paraprotein binding of ionized calcium, which initiates secretion of parathormone (PTH) from the parathyroid gland. PTH acts directly on the bone to increase serum calcium concentration.<sup>11</sup>

Survey radiographs may reveal focal, multifocal, or diffuse osteoporosis-type lesions approximately 3-4 weeks after bone changes have occurred (Fig. 1).<sup>8,11</sup> Clinically, the patient may present with pathologic fractures, rear limb lameness or paresis, or bone pain. Myelograms are an effective means of visualizing the changes to vertebral bodies, especially when the patient presents with rear limb lameness or paresis. Most commonly, the myelogram will show extradural compression of spinal cord in the area of the lesion.<sup>8,9,11</sup> Plasma cell tumors producing IgM often infiltrate the spleen, liver, and lymph tissue rather than bone.<sup>11</sup> Whole body survey radiographs may detect enlargement of these organs and tissues.

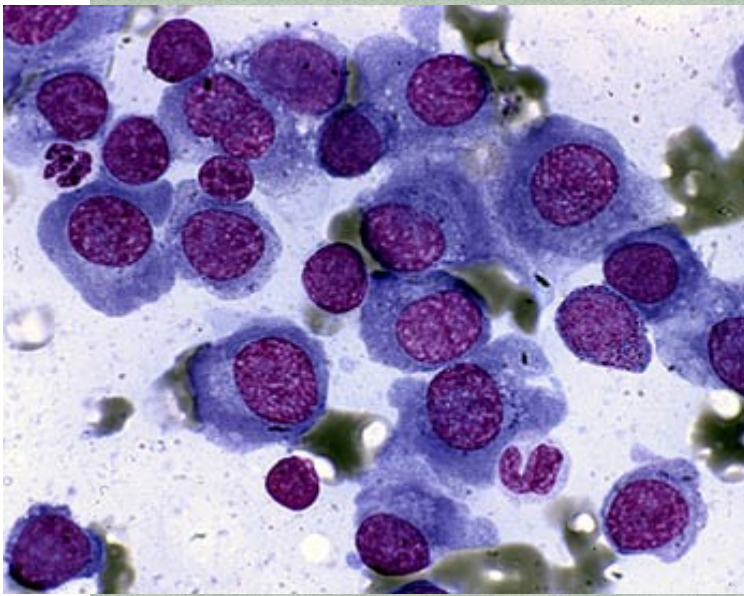


**Figure 1.** Radiograph of an isolated lumbar vertebra from a dog with multiple myeloma. Focal osteolysis is present in the vertebral body (arrows; © Noah's Arkive, The University of Georgia).

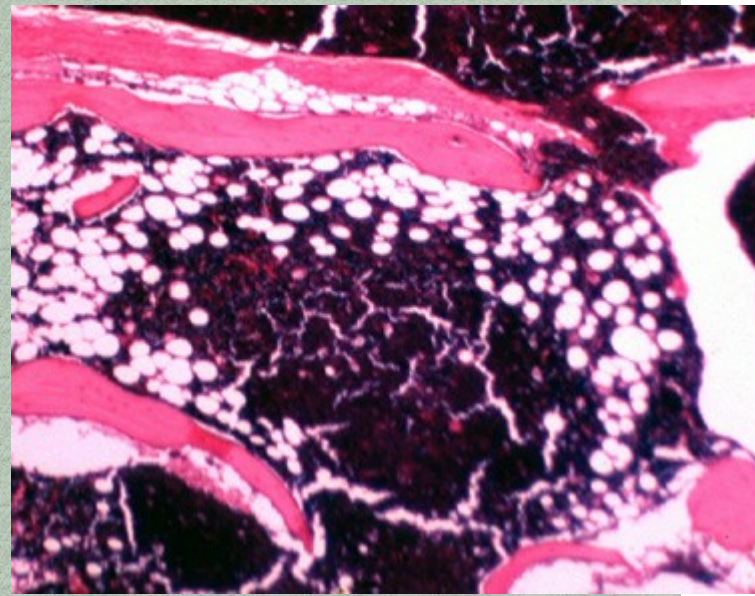
### **Bone Marrow Aspirates with > 20% Plasma Cells**

Bone marrow analysis is an essential procedure when multiple myeloma is suspected. Diagnosis is facilitated by taking aspiration and core marrow biopsies from areas of osteolysis. Cytologic evaluation of the bone marrow should reveal 5% or more plasma cells per smear,<sup>3</sup> or plasma cells should constitute > 20% of all nucleated cells (Fig. 2).<sup>5</sup> However, conditions other than multiple myeloma also can cause plasmacytosis in the bone marrow. These conditions include chronic antigenic stimulation with infectious agents such as *Ehrlichia canis*. The bone marrow core biopsy is more specific because it can demonstrate aggregates of plasma cells in marrow tissue. The presence of large aggregates or sheets of plasma cells within the marrow is highly suggestive of multiple myeloma, if not diagnostic.<sup>3</sup>





**Figure 2.** Bone marrow aspirate from a dog with multiple myeloma that contains many plasma cells (Wright-Leishman stain).

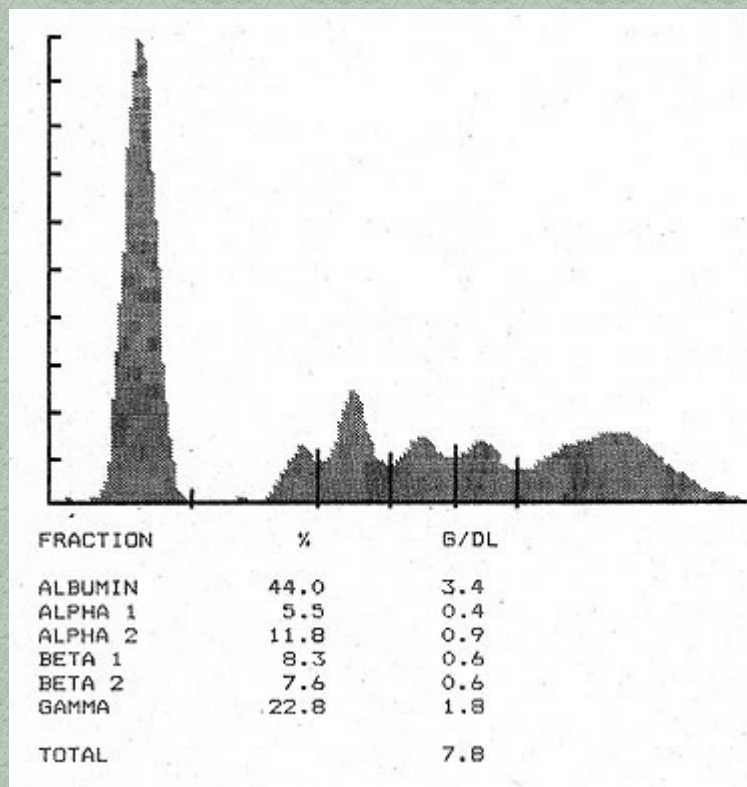


**Figure 3.** Bone marrow core biopsy from a dog with multiple myeloma. Sheets of neoplastic plasma cells and osteolysis are evident (decalcified tissue section with hematoxylin and eosin stain).

### **Hyperproteinemia with Monoclonal Gammopathy**

Hyperproteinemia can be easily detected in plasma or serum by refractometry, but the class of proteins responsible for this change cannot be identified with this technique. The biochemical profile provides more precise information concerning the albumin and globulin concentrations and ratio. In monoclonal gammopathy, the A/G (albumin to globulin) ratio usually decreases due to a massive increase in globulins. The albumin concentration is within the reference interval or slightly decreased.<sup>5</sup> However, changes within the different globulin classes cannot be evaluated unless serum protein electrophoresis is performed. Therefore, serum electrophoresis should be performed on all patients that present with hyperproteinemia and signs suggestive of multiple myeloma.

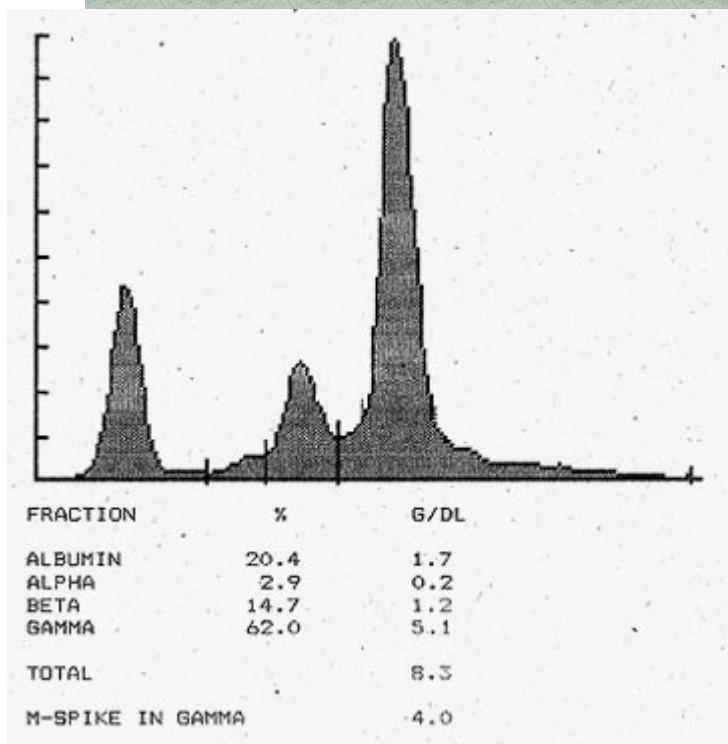
Serum electrophoresis will separate proteins into four major fractions by movement of charged proteins in an electrical field (Fig. 4).<sup>10</sup> The most negatively charged, homogeneous protein is albumin which migrates toward the anode (positively charged electrode). The other three protein fractions migrate toward the cathode (negatively charged electrode) and are separated into the alpha-, beta-, and gamma-globulins according to their electrophoretic mobility. Most immunoglobulins are found in the gamma-globulin fraction; however, IgM is most often associated with the beta-globulin portion of the electrophoretic pattern.<sup>7</sup>



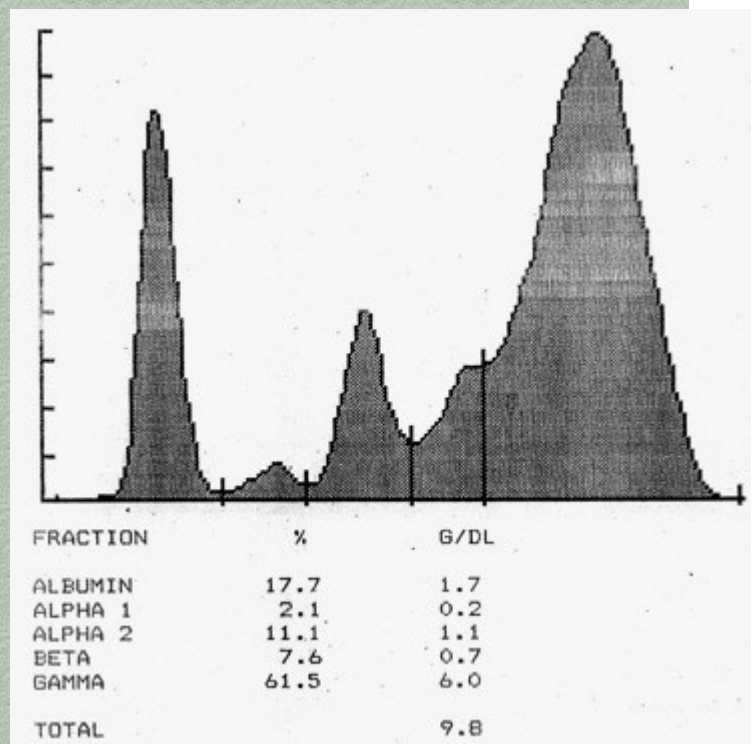
**Figure 4.** Serum protein electrophoretogram from a healthy dog. The peaks, from left to right, are albumin, alpha-1 globulin, alpha-2 globulin, beta-1, globulin, beta-2 globulin, and gamma-globulin.

A monoclonal gammopathy will appear as a sharp, well-defined peak in the gamma-globulin (and less commonly the beta-globulin) range of the electrophoretogram (Fig. 5).<sup>10</sup> The width of the peak is similar to or narrower than that of albumin. The presence of a monoclonal gammopathy is most commonly associated with multiple myeloma; however, other possibilities include lymphosarcoma, chronic lymphocytic leukemia, chronic infection, chronic antigenic stimulation (*e.g.*, canine ehrlichiosis and feline infectious peritonitis), and idiopathic monoclonal gammopathies. In most instances, infection and inflammation are associated with polyclonal gammopathy where the wide-based gamma-globulin peak reflects antigenic stimulation of numerous clones of plasma cells (Fig. 6).





**Figure 5.** Monoclonal gammopathy in a dog with multiple myeloma. The gamma-globulin peak (right) is pointed and narrow, approximating the width and appearance of the albumin peak (left).



**Figure 6.** Polyclonal gammopathy in a dog with chronic bacterial infection. The gamma-globulin peak (right) is rounded and broad suggesting antigenic stimulation and antibody production by numerous clones of plasma cells.

### Bence-Jones Proteinuria

Bence-Jones proteins are the small light chains of the immunoglobulin molecule and are produced by malignant plasma cells. These light chains are filtered from the blood by the kidney and excreted in the urine. A major proportion of filtered Bence-Jones protein is resorbed by renal tubular epithelial cells and metabolized.<sup>2</sup> When the renal tubular epithelial cells become saturated with protein, the remainder of the filtered Bence-Jones protein will be excreted in the urine. These light chain proteins are nephrotoxic and may result in renal dysfunction. Bence-Jones protein also may be deposited as primary amyloid that can accumulate in glomeruli and decrease the glomerular filtration rate. Precipitation of Bence-Jones protein in the renal tubules, amyloid deposition in the glomerulus, and nephrocalcinosis from hypercalcemia ultimately may lead to renal failure.

Dipstick analysis of urine will not detect Bence-Jones proteinuria. A variety of laboratory methods currently are available to identify Bence-Jones proteins. Urine electrophoresis (using either agarose or cellulose acetate matrix) is the most commonly used procedure. Immunoelectrophoresis is probably the most sensitive and specific technique to identify kappa or lambda light chains. Regardless of the laboratory method used, albumin should always be visualized on the electrophoretogram to ensure adequate sensitivity and sample loading.<sup>3</sup> Confirmation of Bence-Jones proteinuria also can be accomplished using immunofixation electrophoresis. This technique detects Bence-Jones protein, distinguishes between kappa and lambda light chains, and identifies the heavy chains of IgA, IgM, and IgG.<sup>3</sup> The most common problem with immunofixation electrophoresis is that it detects intact immunoglobulins in the urine that

are unassociated with Bence-Jones protein.<sup>3</sup>

### **Other Clinical and Laboratory Changes**

Hematologic and biochemical changes may among dogs with multiple myeloma. The hemogram may reflect anemia of chronic disorders and increased rouleaux formation. Due to the decreased production of erythrocytes by the bone marrow, patients can present with a chronic, non-regenerative hemolytic anemia. Myelophthisis can result in cytopenia (e.g., neutropenia, thrombocytopenia) and secondary infection. Changes in the leukogram may include neutropenia, left shift, and toxic changes suggestive of secondary infection. Immunosuppression usually is attributed to abnormally high numbers of monoclonal immunoglobulins that suppress the production of normal Ig-complexes.<sup>7</sup> The presence of circulating neoplastic plasma cells rarely is observed (Fig. 7). When neoplastic plasma cells are observed in bone marrow aspirates of blood, they infrequently have a unique appearance where the blue cytoplasm is bordered by a magenta rim. Such cells, referred to as "flaming plasma cells," suggest marked protein or antibody production.



**Figure 7.** Flaming plasma cell in the blood smear of a dog with multiple myeloma (Wright-Leishman stain).

Biochemical abnormalities also may vary from patient to patient depending upon the severity and dissemination of disease. However, hyperproteinemia with a monoclonal gammopathy (see above), hyperviscosity, and hypercalcemia (see above) may be observed with some frequency.

### **Hyperviscosity Syndrome**

Hyperviscosity syndrome is caused by massive hyperproteinemia that



usually is associated with a monoclonal gammopathy. In some instances, immunoglobulins such as IgA may polymerize as dimers and increase plasma viscosity. Hyperglobulinemia associated with a hypoalbuminemia also will cause blood to become viscous secondary to decreased plasma oncotic pressure and loss of the water constituent of blood. This change in composition will alter the cardiovascular system, inducing a hypertension that can have severe side effects. Due to this "sludging" of blood, the heart has to work harder to function properly. Animals may develop a gallop rhythm, left ventricular hypertrophy secondary to the increased cardiac output, and afterload.<sup>11</sup> Impairment of cardiac function can detrimentally affect vascular perfusion and subsequently the body will experience tissue hypoxia.

Hyperviscosity syndrome also may cause bleeding or hemorrhagic diathesis in addition to severe thrombocytopenia. Paraproteins will coat the platelets and decrease membrane reactivity. Platelet factor III does not function properly and the ability of the platelets to adhere to surfaces and aggregate to form clots is drastically decreased.<sup>7</sup> Nearly 50% of patients with clinical hemorrhage will have abnormal prothrombin and partial thromboplastin times, because the paraprotein also will interfere with hemostasis tests.<sup>11</sup>

Erythrocytes also may be coated by the paraproteins, ultimately leading to a hemolytic anemia. Due to the decreased production of erythrocytes by the bone marrow, patients can present with a chronic, non-regenerative hemolytic anemia.

### **Treatment**

Therapy for multiple myeloma can be palliative or curative; however, complete elimination of malignant plasma cells from the bone marrow rarely is achieved. Over 90% of dogs treated with chemotherapy exhibit clinical improvement.<sup>9</sup> Furthermore, remission of the neoplasm may occur for up to 2 years before an eventual relapse occurs. After initiation of chemotherapy, the growth of myeloma cells will enter a plateau phase that remains stable until a drug-resistant cell population emerges.<sup>9</sup> Expansion of this neoplastic cell population is directly associated with the eventual relapse into active disease. The degree and rapidity of plasma cell growth will predict the clinical stage and progression of clinical signs in each individual.<sup>3</sup>

The chemotherapy protocol usually consists of melphalan and prednisone. Melphalan is an alkylating agent with marked myelosuppressive activity. Secondary thrombocytopenia and neutropenia are common clinical findings after initiation of therapy. Therefore, platelet and leukocyte counts should be monitored during treatment. Cyclophosphamide can be used in addition to or as a replacement for melphalan. Cyclophosphamide may be a beneficial substitute for patients with thrombocytopenia. Radiation therapy also can be instituted with relatively good results in cases of isolated tumors.<sup>9</sup>

Supportive therapy is essential in animals with multiple myeloma to



relieve immediate clinical problems. Antibiotics should be given intravenously for secondary infections due to myelosuppression from chemotherapy or immunosuppression secondary to hyperviscosity syndrome. Administration of fluids will combat dehydration and renal dysfunction. Hypercalcemia, if present, should be treated with corticosteroid administration and diuretics to enhance calcium excretion via the urine. Plasmapheresis can lower the paraprotein burden for patients with hyperviscosity syndrome. In this intravenous procedure, a predetermined volume of blood is processed by machine to separate and remove the plasma via centrifugation. The blood is then restored to its original volume with crystalloid fluids and returned to the patient.

Treatment of multiple myeloma may prolong the patient's life up to 2 years if the neoplasm can be placed in remission. However, owners should be counseled that chemotherapy generally is palliative and not curative; relapse of the neoplasm will probably occur at a future date. Side effects of chemotherapy will depend on the drug protocol; however, immunosuppression may be severe enough that life-threatening secondary infections may occur.<sup>11</sup> Patient prognosis will depend on the clinical syndromes present prior to initiating therapy. Hypercalcemia, Bence-Jones proteinuria, renal insufficiency, and extensive osteolysis are associated with a poorer prognosis and shorter median survival time post-treatment.<sup>3</sup>

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