The plasma cell is of lymphoid lineage and specifically a terminally differentiated B-lymphocyte. Based upon its origin, plasma cells have the capacity to produce immunoglobulins, which under physiologic conditions preserve immune competence and protect the host organism from extracellular pathogens. Like any normal cell, malignant transformation can occur and give rise to a cancerous population of plasma cells. There are a number of disease conditions comprised of malignant plasma cells and include multiple myeloma (MM), solitary osseous plasmacytoma (SOP), extramedullary plasmacytoma, and in felines a syndrome known as myeloma-related disorder in which cancerous plasma cells infiltrate visceral organs.

In dogs and cats, the cause of plasma cell cancers is largely undetermined; however, given the role of plasma cells in mucosal immunity, there has been some speculation that chronic antigen stimulation might promote the development of these malignancies. Anecdotal and clinical support for this speculation would be the common anatomic regions affected by plasma cell tumors including the interdigital regions, oral cavity, and gastrointestinal tract, which are systems commonly in contact with environmental antigens. Multiple myeloma is the most common plasma cell malignancies to cause systemic signs of illness, and will be the focus of this review.

**Pathology and natural behavior**

Clonal origin plasma cell proliferating systemically (usually within multiple bone marrow sites) producing immunoglobulin. Neoplastic cell of origin is the terminally differentiated B-lymphocyte (plasma cell), which normal function is to produce specific immunoglobulin to recognize pathogenic antigens (neutralization, agglutination, and opsonization).

Physical appearance of the cells varies markedly between patients (can be very bizarre). Immunoglobulin produced in excess (a.k.a. M component or paraprotein), usually complete immunoglobulin but sometimes just a portion of the molecule (light chains only = Bence Jones protein, heavy chains only = heavy chain disease). Remember that fully function immunoglobulin is a heterodimer (2 light chains binding with 2 heavy chains).

The M component is usually IgG or IgA. If the M component is IgM, it is called macroglobulinemia or Waldenstrom’s macroglobulinemia. Cryoglobulins are paraproteins that precipitate at temperatures <37°C, causing cutaneous lesions in extremities (colder areas). The M component can cause multiple problems for the patient. Infection is a major problem, and arises because excessive production of the paraprotein inhibits production of normal immunoglobulin, patients are considered to be ‘immunologic cripples’. Hyperviscosity syndrome arises secondary to the massive amounts of paraprotein present. The severity of the serum hyperviscosity is related to the type, size, shape and concentration of the M component. Hyperviscosity necessitates increased perfusion pressure to maintain vascular flow and also causes hypervolemia both of which increase the cardiac workload and can cause cardiomegaly. Combine this with myocardial hypoxia secondary to poor vascular perfusion and heart failure may result. Neurologic abnormalities including lethargy, ataxia and seizures occur because of poor perfusion. Bleeding problems (hemorrhagic diathesis) occur in about 1/3 of dogs with myeloma.

Bleeding may be caused by M-components 1) inhibiting platelet aggregation and release of activating factors 2) adsorbing minor clotting proteins 3) generating abnormal fibrin polymerization 4) producing a functional decrease in calcium. Thrombocytopenia will play a role in bleeding also. Renal failure can be caused by the high protein content in the glomerular filtrate, as a consequence of tubular obstruction by proteinaceous casts, amyloidosis, ascending pyelonephritis, tumor
infiltration, and decreased perfusion secondary to hyperviscosity. Retinal lesions are another sequela of hyperviscosity. Changes include dilated and tortuous retinal vessels and retinal hemorrhages.

**History and physical examination**

Animals may present with nonspecific signs of weakness, PU/PD, pain, lethargy, or inappetance. More specific signs include epistaxis and gingival bleeding or signs due to a compressive lesion or fracture. Rarely, dogs will present with neurologic signs. PE is often nonspecific, try to localize pain if possible (palpate along limbs and spine).

- **CBC** may reveal anemia (secondary to either anemia of chronic disease, blood loss, or red blood cell destruction secondary to high serum viscosity, or myelophthisis).
  - Neutropenia and thrombocytopenia will be seen first if myelophthisis is present.
  - Thrombocytopenia may also be immune-mediated.
- **Serum chemistry** will show hyperglobulinemia (> 90%) and hypercalcemia (15 - 20%). Renal failure is seen in 33-50% of dogs (secondary to poor perfusion).
- **Serum electrophoresis** should be performed to characterize the globulinemia as monoclonal or polyclonal.
- **Urinary analysis** can be evaluated for Bence-Jones proteins. This requires heat precipitation or electrophoresis, as commercial urine dipstick methods will not detect these proteins.
- **Bone marrow aspirate** reveals > 10% infiltration of plasma cells.
- **Survey skeletal radiographs** evaluating specifically for osteolytic (punched out) lesions. Sites most commonly affected include the vertebral bodies, ribs, pelvis, skull and proximal long bones.
  - Biopsy or fine needle aspirate of osteolytic lesions may be needed for diagnosis.
- Demonstration of two or more of the following strongly supports the diagnosis:
  1. Bone marrow plasmacytosis
  2. Presence of osteolytic bone lesions (No osteoproliferation)
  3. Hyperglobulinemia with monoclonal gammopathy
  4. Bence-Jones proteinuria

**Prognostic factors**

Negative prognostic factors are somewhat intuitive and include:

- Hypercalcemia
- Bence-Jones proteinuria
- Extensive osteolytic bone lesions
- Renal Failure
- Severe hyperviscosity

**Treatments options and long term prognosis**

- **Fluid therapy**
  - Intravenous fluid therapy is often needed initially to correct dehydration, improve cardiovascular status, and manage hypercalcemia and azotemia. Treatment with isotonic saline solution is preferred over other fluids in the initial management of hypercalcemic patients.
- **Antibiotics**
  - Antibiotic therapy may be needed to treat concurrent infections, such as urinary tract infection or bacterial pyoderma, as these can progress to life-threatening infections if left untreated.
- **Palliative radiation**
  - Neoplastic plasma cells are sensitive to irradiation, and radiation therapy is a highly effective palliative treatment for MM since it can relieve discomfort and quickly decrease the tumor burden. Indications for radiation therapy include painful bone lesions, spinal cord compression, pathologic fracture (after fracture stabilization), or a large soft tissue mass.
- **Bisphosphonates**
  - Bisphosphonates, such as pamidronate, may be useful in managing hypercalcemia as well as decreasing osteoclastic bone resorption and bone pain. The recommended dose of pamidronate is 1 to 2 mg/kg given intravenously in dogs and, anecdotally, 1 mg/kg given intravenously in cats every 21 to 28 days. Prior to administration, evaluate renal function; dilute the pamidronate in saline solution (amount based on the size of
the patient) and administer as a slow infusion over two hours to minimize renal toxicities.

Aminobisphosphonates are an essential component of therapy for MM in people, and their use is associated with significantly reduced skeletal-related events and improved survival in some studies.

- **Analgesics**
  - Dogs and cats with MM may experience moderate to severe pain; treating for this pain is a priority. Pain may be relieved by treating the underlying cancer and providing various analgesic therapies and supportive care.

- **Chemotherapy**
  - Although a cure is unlikely, MM can be a rewarding disease to treat since chemotherapy can greatly extend the quality and duration of life. The chemotherapy drugs most often used are alkylating agents, usually melphalan, combined with corticosteroids. However, eventual relapse during therapy is anticipated.
  - The overall response rate for dogs treated with melphalan and prednisone chemotherapy is 92%, with 43% of dogs achieving a complete response and 49% achieving a partial response. The median survival time of dogs treated with this drug combination is 540 days, which is significantly longer than the survival time of 220 days in dogs treated with prednisone alone.