MULTIPLE MYELOMA IN THE FELINE

Clinicopathologic Conference

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Introduction

Multiple myeloma is a malignant tumor of plamsa cells that occurs in older animals within the bone marrow (Maxie). Differentiated B lymphocytes undergo a malignant transformation that causes a variety of clinical pathologies, multiple myeloma being one (Appel, Fikry). Clinical conditions caused by multiple myeloma include hyperviscosity syndrome, hypercalcemia, renal disease, anemia, and an increased bacterial infection susceptibility. Cardiac disease has also been associated with multiple myeloma (Sternberg). The cause for the mutation of the plasma cells in unknown among animals, but is believed to be due to carcinogenic exposure to chemicals in humans (Fikry).

Multiple myeloma accounts for less than 8% of hematopoietic tumors in dogs and is even less common in cats, some reporting less than 1% (Fikry). There has been no connection to feline immunodeficiency virus, feline leukemia virus, or feline infectious peritonitis as with lymphoma. Breed and sex are not a predilection, but the disease tends to affect median to older age dogs and cats (Fikry, Sternberg, Appel).

Treatment options for multiple myeloma include supportive care as well as chemotherapeutic agents. The prognosis of this disease depends on the treatment plan and the stage of the disease. Dogs respond better to treatment as cats usually have a more aggressive form of the disease (Cannon).

History and Presentation

Rajah is a 14-year-old, neutered male, domestic short hair that presented to Mississippi State University Veterinary Specialty Center for being down in the hind end. He had a wobbly gait since he was a kitten. He had recently begun dragging his back end. He experienced weight

loss, decreased appetite, but was not painful in the back end. Referring complete blood count and chemistry revealed increased hemoglobin (17.7 g/dL), increased total protein (10.1 g/dL), and increased globulins (7.0 g/dL). General physical exam was within normal limits other than an enlarged bladder that was easily expressed. Neurologic exam revealed normal cranial nerves and reflexes. He was non-ambulatory paraparetic, with the left being worse than the right. Extensor postural thrust was absent in both hind limbs and tail tone was decreased. Severe muscle atrophy was present in both hind limbs. Neurolocalization was determined to be T3 to caudal myelopathy. Further advanced imaging was recommended but was declined. A definitive diagnosis was not apparent at that time.

Five months after presentation to Mississippi State University Veterinary Specialty Center, Rajah was brought into the Pathology department after passing at home for a necropsy. On presentation, he had a body condition score of 2/9. External exam revealed extreme hind limb atrophy. There was a yellow, creamy appearance around his genital area. There was a slightly yellowed appearance to his skin throughout the whole body. The blood appeared thin and did not clot. Examination of the thoracic cavity revealed 300 ml of red-tinged fluid. The lungs were reddened and atelectatic cranioventrally. The left atrium of the heart was enlarged, and it weighed 25 grams. The ventricular wall was thickened with a narrowed lumen. There was an irregularly shaped, dark red 4 x 3 x 0.5 cm mass along the ventral aspect of T3-5 thoracic that protruded into the thoracic cavity. This mass invaded the vertebral canal and compressed the spinal cord with visible loss of cord tissue. Another mass similar in appearance measuring 1 x 2 x 0.5 cm was present along L2-3 vertebrae. There were hyperemic areas on the cervical and sacral regions of the spine ventrally. There was also a hyperemic area similar to the ones on the spine present on the skull measuring 3 x 4 mm. The abdomen revealed 10-12 raised nodules

disseminated throughout all lobes ranging from 0.3-1 cm and the liver was mildly enlarged. The bladder wall was thickened and fully distended containing a large amount of yellow, opaque thick urine. Histopathologic examination revealed neoplastic round cells located in several organs. The cites and organs affected include the vertebral bodies, spleen, liver, bone marrow, and multiple lymph nodes. Other diagnosis based off histopathology include hypertrophic cardiomyopathy and chronic renal disease. There was pleural effusion along with severe pulmonary edema that was chronic. Passive congestion was present in the liver as well as extramedullary hematopoiesis which was chronic. The pancreas revealed islet amyloidosis with nodular hyperplasia and interstitial fibrosis. The kidneys had multifocal glomerulosclerosis, proteinuria, tubular necrosis that was severe and chronic. The bone marrow was 60% infiltrated with malignant plasma cells mixed with decreased erythroid cells which is indicative of multiple myeloma. Although Rajah had several disease processes occurring, the cause of death is most likely congestive heart failure with respiratory failure being the ultimate cause based on the lung pathology.

Pathophysiology

With multiple myeloma, B cells mutate into malignant plasma cells called myeloma cells (Maxie). These cells then overproduce immunoglobulin paraproteins or monoclonal proteins. These M-proteins circulate through the blood infiltrating organs and bone marrow (Fikry, Maxie). There are many different pathologies caused by the circulation of these myeloma cells. Hyperviscosity syndrome is caused by the increased paraprotein circulating in the blood. This can cause neurologic signs as well as affect the heart. Hypertrophic cardiomyopathy can result secondary to this syndrome due to the increase work load on the heart. In many case reports of cats with multiple myeloma, two-thirds had cardiomegaly accompanied by a heart murmur

(Cannon). Osteolytic changes are also observed commonly. Radiographs can usually reveal lytic areas that commonly affect the axial skeleton, but can also be seen on long bones (Goda, Maxie). The current theory is increased bone resorption with decreased bone formation due to dysregulation of cytokine production. These lytic lesions can result in hypercalcemia, pathologic fractures, as well as spinal cord compression if severe enough (Maxie). These lesions are most common in dogs, but the pathology causing the lesions in cats is unclear. Hypercalcemia, as previously stated, can show up on a chemistry panel due to the lytic lesions. Another source of this hypercalcemia can be hypercalcemia of malignancy (Maxie). Ionized calcium measurements are needed to confirm this pathology (Cannon). The hypercalcemia can lead to renal disease as a secondary lesion. The excessive paraprotein can form tubular casts leading to obstruction of tubules. Inflammation occurs due to the released of cytokines from these myeloma cells causing further damage to the kidneys (Cannon, Fikry, Patel). Renal mineralization can be the result of hypercalcemia. Hyperviscosity syndrome can also cause secondary lesions to the kidneys such as amyloidosis and decreased renal perfusion. Patients with multiple myeloma are also at an increased risk of bacterial infections. These infections can become life-threatening due to the compromised function of B cells and immunoglobulin caused by the neoplasia (Maxie).

Diagnostic Approach/Considerations

Several diagnostic modalities are necessary to definitively diagnose multiple myeloma. There is a criterion based from human medicine where at least two of the five must be met for a diagnosis. These are as follows: Monoclonal gammopathy or paraproteinemia, radiographic evidence of osteolytic bone lesions, greater than 5% neoplastic cells or greater than 10% plasma cells in the bone marrow, immunoglobulin light chain (Bence-Jones) proteinuria, plasma cell infiltration of visceral organs in cats (Goda, Maxie, Patel). Radiographs are gold standard for

finding lytic lesions associated with multiple myeloma (Cannon). Ultrasound can be used to identify infiltrative disease in organs commonly affected such as the liver and spleen. Computed tomography and magnetic resonance imaging may also be used, but is often not necessary. Bone lesions are reported it 50% of dogs and 60% of cats diagnosed with this disease (Goda). Complete blood count and a blood chemistry often assists in supporting a diagnosis of multiple myeloma. Due to the mutation of B cells which produce the excessive immunoglobulin and paraprotein, hyperproteinemia and hyperglobulinemia are often apparent on blood results (Cannon, Fikry, Maxie, Patel). Complete blood counts usually reveal a nonregenerative anemia in about 70% of cases (Patel). Thrombocytopenia and leukopenia may also be present but is less common. Bone marrow aspirates reveal plasmacytosis in 96 to 100% of confirmed cases and is usually a definitive diagnosis based off results (Cannon). A urinalysis can be used to determine the presence of Bence-Jones proteins. These light-chain proteins can be found in about two-thirds of confirmed cases of multiple myeloma (Goda, Patel).

Radiographs and advanced imaging were declined for Rajah, but the blood chemistry revealed hyperproteinemia and hyperglobulinemia. These findings met only one of the criteria for diagnosing multiple myeloma. Blood calcium levels for Rajah were normal as well as leukocyte values. All other diagnostics offered were also declined and the owners elected to give supportive care to Rajah at home although there was not a definitive diagnosis for him. The necropsy later revealed plasmacytosis in the bone marrow of greater than 10 percent. The mass and lytic lesions on the axial skeleton also meets additional criteria for the diagnosis. Rajah did have metastatic lesions to the liver, kidney, and spleen which supports the visceral organ infiltration of the disease. Although his urine was not assessed for Bence-Jones proteins, he met four out of the five criteria for a definitive diagnosis of multiple myeloma. The appearance of

Rajah's urine and thickened bladder wall was indicative of a chronic bladder infection and histology revealed *Enterococcus faecalis* to support this finding. Since multiple myeloma increases the risk of bacterial infections, this pathology was most likely due to the primary disease.

Treatment and Management

Supportive care and medical management are often the first steps of treatment. Fluid therapy to correct dehydration will also assist in managing the hypercalcemia and cardiovascular status of the patient especially if hyperviscosity syndrome is present (Cannon). Since bacterial infections can be life threatening, antibiotic therapy may be needed. Multiple myeloma is a very painful disease process especially when boney lesions are present. Analgesics should be of priority for pain relief of the patient (Cannon, Fikry). Radiation therapy is very effective against multiple myeloma. It can help to reduce tumor size which may relieve discomfort and reduce spinal cord compression. Bisphosphonates can also be used to reduce blood calcium by decreasing osteoclastic bone resorption (Cannon). Since this medication can be nephrotoxic, it is to be given, diluted, over a two-hour period to minimize toxicosis (Cannon).

Chemotherapy may be used as a modality since it responds well. The most common combination of pharmaceuticals is melphalan (alkylating agent) in combination with prednisone (Cannon). This treatment can extend life and improve quality of life although relapse will occur. This preferred chemotherapy treatment is most helpful in dogs who show more improvement, but cats do benefit from the treatment as well. Cats tend to be affected by the side effects of myelosuppression and leukopenia more than dogs as well (Cannon). Other chemotherapeutic agents may be used in conjunction with melphalan such as chlorambucil and cyclophosphamide. The recommended treatment in cats is Melphalan at 0.1 mg/kg orally once daily for 10 to 14

days. It is then reduced to every other day at that same dose. Predisone (Prednisolone) is given in conjunction with this medication at 0.5 mg/kg orally once daily (Cannon).

In animals with hind limb paraparesis, it is important to monitor for urinary tract infections. Patients that have spinal compression often have trouble emptying their bladder (Cannon, Fikry). At home monitoring of bladder size and frequent expression of the bladder is necessary for the patient. Keeping the genital region clean and free of debris will help to reduce the risk of urinary tract infections. Access to food and water should be monitored as well. Constant access to water or offering water several times a day is necessary in non-ambulatory patients as dehydration can cause serious complications and even death. Since this is a painful disease process, patients should have activity restricted. If ambulatory, these patients are at increased risk of pathologic fractures due to the lytic lesions of long bones. Supportive care at home and medical management will help to extend quality of life.

Conclusion/Case Outcome

Multiple myeloma is rare in cats and dogs, but fewer cases are reported in cats (Fikry, Maxie, Patel). Prognosis for multiple myeloma is guarded to poor in cats and fair to guarded in dogs that receive treatment. Although dogs respond relatively well to chemotherapy (92% with about 50% remission rate), cats usually possess a more aggressive form of the disease (Cannon). With therapy, dogs can have a survival time up to one and a half years. Cats with a less aggressive form can live up to a year with treatment, but the aggressive form has a grave prognosis with only days of survival time after diagnosis (Cannon). Patients that respond have improved clinical signs and blood value findings. Complete remission is considered when normal globulin levels are present or there is no detectable monoclonal immunoglobulin. Partial remission can be defined by a 50% decrease in globulin levels (Cannon, Fikry).

Although Rajah's owners did not seek further diagnostics and treatments, he was managed at home until his passing. Given the necropsy findings of lesions in the liver, other visceral organs, and the large mass on the spine, Rajah likely had an aggressive form of multiple myeloma that most likely would not have responded well to treatment. His myelomalacia secondary to the large spinal mass also decreased his prognosis for positive response to treatment. The ultimate cause of death was likely respiratory failure secondary to his hypertrophic cardiomyopathy. With his multiple disease processes combined, treatment for multiple myeloma would have likely been unsuccessful.

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