A Sparkling Demise:

Multiple Myeloma in the canine patient

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Introduction:

Multiple myeloma is an uncommon neoplasia accounting for <1% of all malignancies seen in animals. [9] It is most commonly diagnosed in companion animals with more cases seen in dogs than cats. [11] The median age of animals diagnosed with multiple myeloma is 8-9 years old. [9] There is no longer thought to be a sex predilection with this neoplasm; however, early studies suggested that there may have been a higher incidence in males. [11] One study suggested that German Shepard Dogs were predisposed to developing multiple myeloma, but this was likely due to an overrepresentation in the study rather than an increased risk in this breed.[2] Due to the rarity of this condition in veterinary medicine, a significant amount of research is extrapolated from the human literature. Although the etiology of this disease is largely unknown, genetic predisposition, molecular aberration, viral infection, chronic immune stimulation, and exposure to carcinogens have been postulated to contribute to the development of this disease process.[5] Within rodent models, exposure to silicone gel has been associated with the development of multiple myeloma. [11]

Case Report:

Sparky, an approximately 4-year-old neutered male feist presented to Mississippi State University College of Veterinary Medicine (MSU-CVM) emergency service on May 16th 2017 for abdominal discomfort, lethargy and hematochezia. He was diagnosed by a referral veterinarian as having a cecal inversion after a 7 day duration of lethargy, anorexia, and diarrhea. During the week leading up to his referral, he was treated for suspected intestinal parasitism with Drontal Plus and started on metronidazole. Sparky showed no improvements and was referred to a tertiary care facility to pursue further diagnostics. During this visit a colonoscopy was performed and Sparky was diagnosed with a cecal inversion and referred to MSU-CVM

emergency services for possible surgery. Sparky had previously been treated for heartworms when he was adopted several years prior and had no other significant medical history. He was up-to-date on his vaccinations and maintained on a monthly heartworm preventative.

On presentation Sparky was anxious, alert and responsive. He was tense upon abdominal palpation and moderately overweight with a body condition score of 7/9. Sparky had tacky mucous membranes with a delayed capillary refill time of 2 seconds. The remainder of his vitals were within normal limits (temperature: 102.2 *F, heart rate: 92 beats per minute, respiratory rate: 30 breaths per minute) and no other abnormalities were noted on initial physical examination.

An abdominal focused assessment with sonography in trauma (aFAST) scan was performed revealing a hyperechoic splenic nodule. Abdominal radiographs were largely unremarkable and revealed an ill-defined, smoothly marginated, ovoid approximately 1.2 x 2.5 cm soft tissue nodule at the cranial aspect of the tail of the spleen. The spleen was mildly enlarged with rounded margins. A chemistry profile was performed and these results revealed a moderate hypercalcemia of 13.2 mg/dl, a severe hyperproteinemia of 12.3 g/dl, a severe hyperglobulinemia of 10.4 g/dl, and a moderate hypoalbuminemia of 1.9 g/dl. Blood lactate was within normal limits at 0.7 mmol/L. A complete blood count revealed a mild thrombocytopenia of 149 K/ul.

Based on ongoing abdominal discomfort and suspect cecal inversion Sparky was taken to emergency surgery for an exploratory laparotomy. The abdominal exploratory revealed an enlarged spleen and an approximately 4 cm diameter mass on the cecum. The cecal branches of the ileocecal artery were ligated, and a typhlectomy was performed using a thoracoabdominal

stapler. The stapler was then removed and the stapled end was over-sewn using a Cushing's pattern and 3-0 PDS suture material. The abdomen was closed routinely in 3 layers.

Sparky recovered uneventfully in ICU overnight and his incision was iced every 8 hours, he was given IV methadone for post-operative pain control. The following morning he was weaned off methadone and switched to oral Tylenol 4. Post operatively he had a decreased appetite and was licking his lips, so mirtazipine was added as an appetite stimulant and both maropitant and ondansetron were added as antiemetics. Sparky's appetite waxed and waned while being hospitalized.

On 5/18/17 the cecal histopathology revealed well differentiated plasma cells with a mitotic rate of 6 per high powered field, neoplastic cells extending through the lamina propria, tunica, submucosa and transmurally with clean surgical margins. These results were suggestive of an alimentary plasma cell tumor which can be associated with multiple myeloma. Typically solitary osseous plasmacytomas and extramedullary plasmacytomas behave more aggressively than cutaneous, oral and colorectal plasmacytomas. [9] Due to the aggressive behavior of this neoplasia further diagnostics were pursued to check for possible metastasis. On 5/19/17 abdominal and thoracic radiographs were performed to fully stage his neoplasm. No bony lysis was detected radiographically.

On 5/21/17 and 5/22/17, Sparky was guarding his neck and intermittently vocalizing. Neck pain was suspected, thus he was started on gabapentin for neuropathic pain and diazepam as a muscle relaxant. He was then switched from Tylenol 4 to tramadol in attempt to establish more effective pain control. His pain level increased after switching medications so an IV catheter was placed and he was readmitted to the ICU for intravenous pain control with methadone. His appetite improved while on intravenous pain control overnight and he passed a

large volume of pasty yellow feces and was placed on metronidazole. Unfortunately, no matter the progress that was made, setbacks were encountered in controlling Sparky's pain. An attempt to reduce Sparky's methadone dosing interval was unsuccessful causing him to become markedly depressed and painful, after which he was placed on a ketamine constant rate infusion for adjunctive analgesia.

Since the time of initial presentation, Sparky's serum calcium rose from 13.2 mg/dl to 15 mg/dl on 5/23/17. Hypercalcemia is evident in 15-20% of all cases of multiple myeloma. [11] One proposed mechanism for this manifestation is that neoplastic cells produce osteoclast stimulating substances, which lead to the release of calcium from bone stores.[8] According to the human literature malignant bone marrow plasma cells influence bone homeostasis through production of IL-3, decoy receptor protein 3, macrophage inflammatory protein-1α (MIP-1α), MIP-1β, and TNF- α. [1] Production of these factors causes osteoclastic activation and osteoblastic inhibition, ultimately leading to bone pain. [1] In order to reduce bone pain, Sparky was started on an IV infusion of pamidronate. Pamidronate is a bisphosphonate that works to inhibit osteoclastic activity. Recent studies from human literature reveal that bisphosphonates will reduce hypercalcemia and the skeletal complications from this disease.[11] After receiving a pamidronate intravenous infusion on 5/25/17 Sparky's hypercalcemia decreased and normalized from 15 mg/dl on 5/23/17 to 9.4 mg/dl on 5/29/17.

By day 7 of Sparky's stay, his pain continued to be uncontrolled and focused primarily on his neck region. Cervical radiographs were performed and were largely unremarkable revealing a hypoplastic dens. Due to his increased cervical pain, high suspicion of multiple myeloma, and lack of radiographic lesions, a CT and bone marrow biopsy were performed under general anesthesia. In human medicine, a CT is recommended for staging multiple myeloma, however

consistent staging recommendations do not exist in veterinary medicine.[11] The CT revealed ill-defined, irregularly marginated, variably sized and shaped multifocal regions of moth eaten medullary lysis of the occipital bone, vertebral bodies of the cervical spine, vertebral bodies of the viewable thoracic spine, the scapulae, and humeri. There was also soft tissue attenuating, contrast enhancing material at the vertebral body of C4 and C5 causing dorsal deviation of the spinal cord. The bone marrow biopsy of the left proximal humerus revealed monomorphic collections of plasma cells with large Golgi body areas, hyperchromatic nuclei with dispersed chromatin, and large prominent nucleoli. The cytology revealed large round to oval cells with dark basophilic cytoplasm consistent with multiple myeloma.

Definitive diagnosis of multiple myeloma is based on having two of the following conditions: radiographic evidence of osteolytic lesions, a bone marrow biopsy with greater than 20% plasma cells (or >10% with cellular atypia), a monoclonal gammopathy seen in either urine or serum and a Bence Jones (light chain) proteinuria.[1] The osteolytic lesions on CT, the monomorphic plasma cell population on the bone marrow biopsy, and the cecal alimentary plasma cell tumor confirmed Sparky's diagnosis of multiple myeloma. Sparky's hyperglobulinemia, hyperproteinemia, hypercalcemia, and proteinuria evident on lab work supported this diagnosis. Diagnosis in humans is typically based on having one major and one minor criteria; however the gold standard for identification of M-protein is immunofixation.[11] Malignant plasma cells produce an overabundance of the immunoglobulin which is known as the M component, which can be an entire immunoglobulin (IgG, IgA) or a portion of the molecule such as the light chain.[10] In normal conditions heavy and light chains are balanced, but with multiple myeloma there is an excess of light chains which have a low molecular weight. [11] As a result, light chains may result in proteinuria and cause renal damage. [2] The major criteria consists

of a tissue plasmacytoma, >30% bone marrow plasma cells, or a serum monoclonal gammopathy of >3.5 g/dl IgG or > 2 g/dl IgA.[10] The minor criteria consists of 10-30% bone marrow plasma cells, lytic lesions or a lower monoclonal gammopathy.[10] In humans, Bence Jones proteinuria, hypercalcemia and osteolytic lesions are negative prognostic indicators. [4]

Sparky's urinalysis revealed isosthenuria (1.010 mg/dl) and 3+ proteinuria. Due to the suspicion of increased light chains in his urine resulting from a suspect multiple myeloma, Bence Jones protein test was sent out. This test revealed a positive screening test but a negative confirmatory test. A negative result could be due to a low sample concentration, myeloma cells secreting intact immunoglobulins instead of the light chain, sample bacterial contamination or poor refrigeration technique.[3] Only 25-40% of multiple myeloma cases have Bence Jones proteinuria. [11]

On 5/28/17 Sparky became ambulatory paraparetic and required a sling for more support. Paresis has been reported in cats with multiple myeloma secondary to osteolysis of lumbar vertebral bodies or extradural compression.[10] The following day melphalan, a chemotherapeutic alkylating agent, was started at 0.2mg/kg orally every 48 hours. Melphalan interferes with RNA transcription and DNA replication to disrupt nucleic acid function. [8] Therefore this chemotherapeutic agent has effects on both dividing and non-dividing cells. [8]

Typically the most effective treatment, with a 92 % response rate, is a combination of melphalan with prednisone, as prednisone is thought to increase the efficacy of melphalan.[10] Melphalan is an alkalating agent that aims to reduce myeloma cell burden, alleviate bone pain, enable skeletal healing and reduce serum immunoglobulins. It is generally well tolerated, and the main adverse effect is irreversible thrombocytopenia.[4] Therapy is continued throughout the dog's lifetime and adjusted based on myelosuppression or relapse of clinical signs.[11]

Cyclophosphamide has been identified as an alternative alkylating agent and can be used in dogs with severe systemic involvement, or severe thrombocytopenia.[11] When dogs relapse or are initially resistant to melphalan therapy, the VAD protocol (vincrisitine, doxorubricin and dexamethasone SP) is recommended as a second line therapy.[11] Most dogs respond to this therapy initially; however typically the response lasts only a few months. Improvement of bone pain, lameness, lethargy and anorexia should be seen in 3-4 weeks after starting chemotherapy.[11]

On 5/30/17 Sparky continued to have a poor appetite and began to vocalize even when approaching his kennel and he was transferred to the MSU-CVM Oncology Services for further treatment. A fentanyl CRI was added as multi-modal pain control. From 6/1/17-6/3/17 Sparky's pain level appeared to be decreased and he had improved motor function in his hind end and vocalized much less frequently.

Due to his prolonged stay in the hospital and fluctuating pain level, his owner's hoped to take him home. Since his pain control continued to improve with melphalan therapy, he was weaned off injectable pain control and discharged on 6/5/17. He was sent home on maropitant, mirtazapine, metronidazole, diazepam, gabapentin, melphalan and a tapering dose of prednisone.

Case Outcome

On 6/19/17 Sparky returned to MSU-CVM Oncology Services for recheck bloodwork. His owners reported that Sparky was doing well at home and was mildly ataxic and still struggled to walk on slick surfaces. Baseline bloodwork was performed prior to initiating melphalan therapy, and repeated during his recheck on 6/19/17, 21 days after initiation of chemotherapy. The changes in his bloodwork from 5/29 to 6/19 reveal a resolved thrombocytopenia of 144 to 208 k/ul, and an unchanged anemia of 26%. Since starting chemotherapy he developed a leukopenia of 3,000/ul. His chemistry changes revealed an

improving hyperproteinemia from 10.4 to 8.2 mg/dl, and an improving hyperglobuinemia 8.5 to 5.1 mg/dl. According to Withrow et al, improvement of hyperglobulinemia, hypercalcemia and a normalized hemogram should be expected in 3-6 weeks after initiation of melphalan therapy.[10] Response to melphalan is considered good when there is a 50% reduction in the pre-treatment values of the M component (Bence Jones proteinuria or immunoglobulin).[11] A Bence Jones protein test can be repeated every month until a sufficient response is noted, after which it is repeated every 2-3 months.[11]

Despite current treatment regimens, multiple myeloma is typically a fatal disease in most species thus research into more effective treatments is ongoing.[11] A case report describes an 11 year old dog presenting for lethargy and anorexia with a monoclonal gammopathy, hypercalcemia, and a splenic plasmacytoma.[10] This dog did not receive surgery and did not have bone pain. He was treated with a single dose of intravenous vincristine and sent home on melphalan and prednisone. After 30 days, the anemia, hyperproteinemia, and hyperglobulinemia had improved and the patient remained in remission for 13 months.[9] In another case report, a 12 year old dog with multiple myeloma presented with a right front lameness that had marked improvement of aggressive bony lesions after 4 months of melphalan and prednisone therapy with complete resolution of lameness after 300 days.[5] A final case of a 4 year old Mastiff that presented for 2 months of lameness showed mild improvement with carprofen. This dog had a monoclonal gammopathy, was hypercalcemic, and bone biopsy of the proximal left tibia revealed multiple myeloma.[7] Initiation of melphalan and prednisone was started and his bone pain and lameness improved over two months. After three months he presented with an acute non-weight bearing lameness, and radiographs revealed a pathologic left tibial fracture ultimately resulting in euthanasia. As illustrated by this final case, osteolytic lesions due to multiple

myeloma take months to improve and are unlikely to resolve.[10] Multiple myeloma can be a rewarding disease to treat as the response rate is impressive; however, complete elimination of neoplastic plasma cells is unrealistic and eventually relapse will occur.

On June 26th, 2017 Sparky presented on emergency to MSU-CVM oncology services as he was uncomfortable and unable to walk unassisted. He was unable to bend his neck down to drink water, was vocalizing, and had multifocal muscle fasciculation. Further diagnostics, such as CT, were offered to further evaluate the progression of his osteolytic lesions, as well as a chemotherapeutic rescue therapy. Due to intractable bone pain, generalized discomfort, and decline in quality of life, euthanasia was elected. A necropsy was not performed so no further gross pathological abnormalities were identified.

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