Finding Nemo's Neoplasia

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Introduction:

Multiple myeloma, a plasma cell neoplasm, is a rare cancer of cats, accounting for less than 1% of feline malignancies.[7] Classically, plasma cell tumors that originate in the bone marrow with or without metastasis to extramedullary sites have been referred to as multiple myeloma; solitary plasma cell tumors of soft tissue organs such as the liver or spleen without intramedullary involvement are referred to as plasmacytomas.[5] However, unlike in dogs and humans, plasma cell disorders in cats often present with extramedullary plasmacytomas (either cutaneous or non-cutaneous) with or without bone marrow involvement. Thus, the more general term "myeloma-related disorders" or "MRDs" have begun to gain favor over "multiple myeloma" when referring to this type of neoplasm in the feline patient.[8] MRDs are typically a disease of older cats around 12-14 years old.[10] Males and females are thought to be equally affected, though some evidence indicates slightly increased predisposition in males. The majority of reported cases have been in the domestic shorthair.[7] There is no apparent correlation with retroviral infection.[5] The following case report of a cat diagnosed with an MRD, or multiple myeloma, will review the history, presentation, clinical signs, diagnostic approach, pathophysiology, and treatment options of this condition in the feline patient. Some comparisons to this condition in the canine will also be addressed.

History and Presentation:

Nemo is a 13-year-old, male neutered Domestic Shorthair who presented to MSU-CVM Oncology on June 9, 2021. Nemo had displayed an approximately two-month course of waxing and waning anorexia and lethargy. He occasionally regurgitated and his stool had become soft-formed. In addition to the non-specific signs, Nemo had originally presented to his primary

veterinarian in May 2021 for a small puncture-like wound on his right thorax from rough-housing with a housemate that was developing into a small abscess. The abscess was drained, and Nemo was given Cerenia, Convenia, buprenorphine and mirtazapine. Several days later, the wound was just beginning to improve, yet Nemo was still anorexic and lethargic and returned to his primary veterinarian. Complete blood count and chemistry panel revealed a marked hyperglobulinemia and mild hypocholesterolemia. Otherwise, findings were consistent with a stress leukogram. Total T4 was within normal limits. Radiographs showed medial deviation of ribs 8 and 9 coinciding with the location of the puncture wound. He was switched to Clavamox and referred for an internal medicine consult.

Before presenting to his internal medicine appointment, however, he presented to Veterinary Specialists of Birmingham (VSB) on emergency for a forelimb lameness which was treated supportively. He kept his appointment several days later with an internist at VSB. Diagnostic imaging revealed possible pancreatitis and possible mild cardiomyopathy, though no overt abnormalities were found to explain his clinical signs. Serum protein electrophoresis was submitted and revealed a narrow monoclonal spike at the gamma globulin fraction. Due to top differentials being some sort of neoplasia, Nemo was referred to MSU-CVM Oncology with instructions to continue the Clavamox and mirtazapine in the interim.

On presentation on June 9, 2021, Nemo was bright, alert and responsive. He weighed 5.6 kilograms with a BCS of 6/9. Vital parameters were within normal limits with a temperature of 102.1F, heart rate of 180 beats per minute and respiratory rate of 32 breaths per minute. His right-sided thorax wound was small, approximately 1 cm by 1 cm and appeared to be mostly healed. There was a grade IV/VI systolic murmur present on auscultation that, according to his records, has been present since he was a kitten. On pulmonary auscultation, no crackles or

wheezes were heard. Peripheral lymph nodes were small, smooth and symmetrical. No other abnormalities were noted on physical exam.

Diagnostic Approach:

Clinical signs and previous diagnostics placed a myeloma-related disorder at the top of the list of differentials. Although variable criteria have been suggested to make a diagnosis of multiple myeloma, there are four key criteria most often used. Two of the four are recommended to be present for a diagnosis of MRD to be made.[7,10] The first is monoclonal gammopathy diagnosed on serum protein electrophoresis. The second is radiographic evidence of skeletal lysis. The third is presence of Bence-Jones proteinuria, the light chain portion of the immunoglobulin which may overflow into the urine. The fourth is >20% marrow plasma cells or >5% marrow plasma cells with evidence of atypia.[1,7] However, as described above, cats may commonly have MRDs caused by extramedullary plasma cell infiltration. Thus, presence of visceral organ involvement has been suggested as a fifth criteria for the feline patient.[6]

For Nemo, a thorough diagnostic plan was developed to look for these criteria in addition to ensuring he was otherwise healthy before initiating treatment. A complete blood count (CBC) and chemistry panel were performed. CBC revealed a moderate lymphopenia and mild anemia with hematocrit of 30%. Platelet count was decreased on the analyzer count but appeared adequate on manual count. Blood chemistry revealed a marked hyperproteinemia characterized by a hyperglobulinemia of 9.1 g/dl. A mild hypocholesterolemia was also present. Other abnormal values were very mild and not clinically relevant. FeLV/FIV Snap test was below detectable limits for both FeLV antigen and FIV antibodies. Urine was submitted to Michigan State Veterinary Diagnostic Laboratory for Bence-Jones proteinuria testing. Although the

screening test was positive, confirmatory testing was negative resulting in an interpretation of negative for Bence-Jones proteinuria.

Abdominal radiographs showed a mild increase in the trabecular pattern of the spinous processes of the cranial lumbar vertebrae which were considered likely to be degenerative changes, but due to the concern for multiple myeloma, neoplasia could not be ruled out as a cause. Thoracic radiographs showed similar changes in the dorsal spinous processes of the thoracic vertebrae as well as the previously described chronic right-sided rib fractures. Abdominal ultrasound revealed hypoechoic structures in the liver most consistent with cysts. Bilaterally hyperechoic renal cortices were attributable to chronic kidney disease, fat deposition, or glomerulonephritis with infiltrating neoplasia as a less likely differential. Changes to the pancreas were consistent with chronic pancreatitis. Echocardiogram showed a mild asymmetric hypertrophic cardiomyopathy of the left ventricular free wall but with minimal functional changes.

Fine needle aspirates of both the liver and spleen were submitted. Liver samples were not diagnostic. Although the sample was not sufficient for diagnosis, splenic samples revealed possible lymphoproliferative disease with low to moderate numbers of plasmacytoid cells.

Nemo was placed under general anesthesia for bone marrow biopsy. Cytology of samples were not cellular enough to evaluate marrow cellularity although no observed cells appeared atypical or inappropriate in proportion. Bone marrow histopathology and immunohistochemical (IHC) staining revealed no evidence of plasma cell neoplasia. The samples revealed small clusters of normal appearing plasma cells with no effacement of normal bone marrow. IHC staining for B cell and plasma cell populations were performed out of an abundance of caution with no abnormal results.

Based on his history and previously diagnosed monoclonal gammopathy, suspicion for an MRD was high. Abdominal and thorax radiographs showed possible lysis in the vertebrae, and splenic cytology showed possible plasma cell infiltration. Due to these findings and the absence of any other likely differential diagnoses that would account for these changes at this time, a presumptive diagnosis of a myeloma-related disorder was made.

Pathophysiology:

The pillars of humoral immunity are terminally-differentiated B lymphocytes or plasma cells and their secreted antibodies. Following primary immunization, the IgM antibody isotype is the first produced by the B cell. Eventually B cells may class switch and produce other forms of immunoglobulin such as IgA, IgG, or IgE. Some of these higher-affinity B lymphocytes migrate back to the bone marrow or other sites of inflammation where they differentiate even further into plasma cells. While effector B cells may produce antibodies, plasma cells are high-volume antibody producers. No matter the class produced, these antibodies consist of four immunoglobulin protein chains – two heavy chains and two light chains.[3]

Myeloma-related disorders develop from transformation of either a plasma cell or precursor B cell lineage that continues to proliferate and forms a neoplastic population that is typically monoclonal and produces homogenous immunoglobulin.[6] What initially causes these cells to undergo neoplastic transformation is unknown. In humans, exposure to various toxins and ionizing radiation are considered risk factors although this has not been directly linked to any feline cases.[1] One study contained a pair of sibling cats, thus a genetic component has been given consideration.[5] There is minimal evidence to suggest development of MRDs is related to chronic inflammation or vaccination, although this theory has been proposed as well.[7] Whatever

the cause, these malignant plasma cells produce large amounts of immunoglobulins, resulting in a hyperglobulinemia that is often marked. Most commonly, these plasma cells produce complete immunoglobulins.[1] The produced immunoglobulin may be of any class, though typically all the same class, resulting in the trademark monoclonal gammopathy.[11] Biclonal gammopathies do occur, however, possibly due to two independent tumor cell lines, isotype switching of one tumor cell line, or spurious causes from dimeric IgA production.[7]

No definitive schema for staging MRDs in cats has been agreed upon, though several have attempted to lay out guidelines. Fikry suggested a division between aggressive and less aggressive based on various clinical signs at presentation and initial response to treatment.[5] Mellor et al. saw a difference in median survival times when evaluating histopathologic, immunohistochemical, and cytologic analysis for degree of differentiation. Simply described, a greater proportion of plasmablasts resulted in poorer prognosis. In humans, well-differentiated tumors are typically not associated with extramedullary involvement. In cats, however, well-differentiated tumors may be found relatively commonly in extramedullary sites with or without bone marrow involvement. Thus, Mellor suggests that the primary tumors in cats may originate in extramedullary or intramedullary sites. This is in stark contrast to the dog and the human, in which intramedullary origin of multiple myeloma is consistently seen with possible metastasis to extramedullary sites in poorly differentiated tumors or later in the disease course.[9]

The presentation of a cat with an MRD is highly variable, both in what clinical signs are present and their severity. The clinical signs associated with this disease are a result of organ or bone infiltration, high levels of circulating globulins (sometimes referred to as the M component) or both.[6] The cat may even be free of clinical signs at the time of diagnosis, with a thorough diagnostic workup initiated on incidental bloodwork findings. Nonspecific signs such as

lethargy, weakness, reduced appetite, vomiting and diarrhea are among the most commonly noted signs at presentation.[8,10] Other signs may include lameness or bone disease, palpable organomegaly, renal disease and azotemia, bleeding diathesis, hypercalcemia, immunodeficiency, various cytopenias, heart failure, neurologic signs and hyperviscosity syndrome.[6,8,10]

Some clinical signs seen with MRD are directly due to the presence and proliferation of the myeloma cells. For example, bone pathology is reported in 8 to 65% of cats. Skeletal lesions have been observed in the vertebrae, ribs, pelvis, skull and metaphases of long bones.[6] Areas of lysis are due to local plasma cell proliferation.[7] These areas may result in no signs, pain or lameness or even pathologic fracture if severe enough.[4] Similarly, palpable organomegaly, typically of the spleen or liver, may occur due to proliferation of the tumor cells in these organs. If the liver is a major site of extramedullary involvement, liver values are often elevated but not always. Unlike in the human and dog, in whom extramedullary involvement is more often considered metastasis of multiple myeloma following origin of the tumor in the bone marrow, feline MRDs may present as an extramedullary plasmacytoma relatively regularly with or without bone marrow involvement.[8] Skin masses have also been reported to cause systemic hyperglobulinemia.[7] Also directly related to presence of the tumor, proliferation of plasma cells in the bone marrow may result in anemia, neutropenia or thrombocytopenia due to myelophthisis. A normocytic, normochromic, non-regenerative anemia is one of the most common bloodwork abnormalities following hyperglobulinemia itself.[6]

Other clinical signs arise from systemic problems associated with the hyperglobulinemia and may be considered paraneoplastic syndromes. Many of the systemic signs are secondary to hyperviscosity of the blood. Hyperviscosity syndrome, or HVS, may result in a vast constellation

of clinical signs including cardiomyopathy, renal disease, bleeding diathesis, neurologic signs and ophthalmic abnormalities. Hypertrophic cardiomyopathy and heart murmurs may be noted secondary to excessive workload and myocardial hypoxia.[6] Cardiac disease, in addition to the hyperviscosity itself, may also predispose patients to thromboembolic disease.[7] Renal insufficiency and azotemia have been noted in approximately 25% of cases, depending on the cited study. It is thought to have a multifactorial pathogenesis related to hypercalcemia, hyperviscosity and the presence of Bence-Jones proteins all potentially causing damage to the kidney.[6,8] The pathogenesis of bleeding diathesis is also multifactorial but includes the thought that the M component may interfere with the coagulation cascade, the endothelium or normal platelet function.[7] The previously mentioned thrombocytopenia may complicate matters further. Anemia may be due to myelophthisis as mentioned above but may instead be caused by – or worsened by – loss from the bleeding diathesis or destruction due to HVS.[6] Neurologic signs, if present, may range from general depression to a coma. Seizures or ataxia may also be present.[7] Ophthalmic exam may reveal dilated or tortuous retinal vessels, retinal hemorrhage or even retinal detachment.[6] It is important to note that although these signs are similar to those associated with hypertension, elevated blood pressure is not a feature of HVS.[7] Hypocholesterolemia has been reported commonly in cats with MRDs as the liver may downregulate production of cholesterol to attempt to maintain a normal oncotic pressure in the face of marked hyperglobulinemia.[10]

Like anemia, hypercalcemia is unique as a clinical feature of myeloma-related disorders in that it may be due to local changes or paraneoplastic effects. Local invasion of the tumor causing bone lysis may release excessive amounts of calcium into the circulation. In addition, production of parathyroid hormone-related peptide has been reported which may cause effects

distant to the tumor that result in elevated calcium. Hypercalcemia should be confirmed with ionized calcium.[7] Elevated calcium may complicate other signs including renal dysfunction or neurologic signs.[1,7] Hypercalcemia has also been associated by some with a more aggressive clinical course.[5] It is not seen in the majority of cases, however, with 10-25% of cats affected.[7]

Immunosuppression may become a major issue for cats with MRDs. As described above, reduction of circulating leukocytes may occur secondary to myelophthisis. In addition, high levels of circulating monoclonal immunoglobulins may decrease functional immunoglobulin levels.[7] Although infectious processes, such as upper respiratory infections and dental disease, have been ongoing in some cats diagnosed with MRDs, overwhelming infection is rarely reported.[1]

Treatment:

The foundation of treatment for feline MRDs is chemotherapy directed at the tumor cell mass itself. Though melphalan is the most used chemotherapeutic agent for multiple myeloma in dogs, cats appear to be highly prone to developing neutropenia with this drug.[4] Thus, many clinicians prefer cyclophosphamide as a first-line treatment for MRDs in cats.[1] Cyclophosphamide is an oral alkylating agent which, in simple terms, cause cross-linking and mismatching of DNA strands.[6] Pill sizes are an issue in the cat. They must be compounded to be able to dose appropriately and are typically sent with the owner for at-home administration. Using reputable compounding pharmacies is always recommended. Burton et al. showed relatively good results for both potency and stability in various compounded cyclophosphamide products.[2] A corticosteroid may or may not be added to this protocol depending on clinician preference and patient signs.[4]

The systemic effects of the tumor should also be assessed and treated as needed. Fluid diuresis for hypercalcemia and azotemia or bisphosphonates if skeletal lesions are present may be considered to name a few. Careful monitoring for infectious processes due to immunosuppression is always warranted.[1,7]

Nemo was started on cyclophosphamide chemotherapy in June 2021. Instructions were given to administer one 25 milligram capsule twice per week (Thursdays and Mondays). His owner was given complete instructions about chemotherapy administration and safety including wearing gloves while handling and never crushing or splitting capsules. Recommendations were made to recheck CBC and globulin levels in two weeks with MSU-CVM Oncology or his referring veterinarian.

Case Outcome:

Dogs with multiple myeloma receiving chemotherapy treatment will often go into a long-term remission. Prognosis for the cat is not typically as favorable. However, over half of cats will respond to chemotherapy treatment and relatively long-term responses of over a year have been reported.[4,6] Cats presenting with a more aggressive form of the disease had a markedly reduced median survival time as opposed to a less aggressive presentation. Median survival times with treatment are typically in the eight-to-thirteen-month range although many factors play a role to influence prognosis.[6,7] Eventually, the tumor may develop resistance to chemotherapy and death will follow due to infection, renal failure, or euthanasia following development of marked bone pain or reduced quality of life.[6] Since these are typically older cats at diagnosis, death that is not attributed to the MRD but to other unrelated causes may occur.[4]

Nemo continued chemotherapy. His packed cell volume and total protein on a complete blood count were monitored at his primary veterinarian every 14 days. He visited MSU-CVM Oncology monthly for complete blood counts and chemistry panels. His anemia persisted for several months as his globulin levels slowly decreased. At his most recent recheck in October 2021, his packed cell volume was normal. His globulin level was mildly elevated but decreased from his September bloodwork. He has lost about one kilogram since his original diagnosis in June. His appetite is variable, and he still receives mirtazapine occasionally to help with this. He otherwise appears to be tolerating his chemotherapy well and often plays with his younger kitten housemates. He was discharged in October with instructions to next recheck with his primary veterinarian in six weeks and to follow up with MSU-CVM Oncology in three months. He still receives twice weekly cyclophosphamide as initially prescribed.

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