Pete's Problem

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Introduction

Histocytes are a subset of leukocytes that have an important role in the immune system. These cells typically divide into two groups, monocyte/macrophages and dendritic cells, and have many surface antigens and receptors for complement and immunoglobulin factors. Monocytes and macrophages are typically phagocytic and play a crucial role in the innate immune system, while dendritic cells act as potent antigen presenting cells in the adaptive immune response. There are several cancers of histiocytic cell lines documented in dogs, all of which should be differentiated as they carry different treatments and outcomes.[1]

History and Presentation

Pete, a 7-year-old male intact English Pointer, presented to MSU-CVM emergency service on February 21, 2019 on referral for a pyothorax. Pete was a bird dog that stayed with his trainer at a training facility in Florida. On February 4, 2019, three weeks prior to presentation, Pete's owner noticed that Pete was breathing harder and was taken to his primary veterinarian. There thoracic radiographs were taken that revealed pleural effusion. Fluid from the thorax was then submitted for analysis along with urine for a urinalysis and blastomycosis testing. On February 6, 2019, fluid analysis showed high nucleated cellularity, with the nucleated cells being predominately (>90%) mildly to moderately degenerate neutrophils with no bacteria seen. Total protein of the fluid measured 3.1 g/dL, nucleated cells measured at 24,130 cells /ul, and red cells totaled at 90,000 cells/ul. The results of the fluid analysis were consistent with a diagnosis of suppurative effusion, consistent with a diagnosis of pyothorax. Urinalysis had 2+ bacteria but was otherwise unremarkable. At that time Pete was started on Baytril (enrofloxacin) and SMZ-TMP (Sulfamethoxazole and trimethoprim) tablets.

A day later, a second set of thoracic radiographs were performed with no improvement, and the result of the EIA Blastomyces antigen testing was negative. On February 12, blood for a complete blood count and a catalyst one test was drawn and submitted. The results of the complete blood count were unremarkable and the catalysts one indicated a mildly decreased glucose at 69 mg/dL (74-143). The following day, results of a culture and sensitivity of the thoracic fluid were obtained. *Corynebacterium* species was isolated and demonstrated sensitivity to all antibiotics tested including trimethoprim/sulfa and amoxicillin/clavulanic acid. Clavamox was then added to Pete's medical treatment. On February 19, three days before presentation to MSU-CVM, a single lateral thoracic radiograph was taken, indicating the placement of a chest tube. During the days following placement of the chest tube, Pete's thorax was drained three to four times daily with approximately 600-1500 milliliters of fluid drained each time.

Pete was referred to MSU-CVM and presented to the emergency service on February 21, 2019. At time of presentation, Pete was bright, alert, and responsive. His temperature was 100.3*F. The remainder of his vital signs, pulse (128 beats per minute) and respiratory rate (36 breaths per minute) were within normal limits. His mucus membranes were pink, and he had a capillary refill time of two seconds. Thoracic auscultation revealed a muffled cardiac sounds and decreased lung sounds ventrally. Pete's blood pressure readings were 192/77 (115), 173/56 (61), and 152/78 (103), respectively. On abdominal and thoracic FAST scan, Pete had no free fluid in his abdomen and severe pleural effusion bilaterally. He was started on fluids at 1.5x maintenance, 1mg/kg of Cerenia IV every 24 hours and 1mg/kg of pantoprazole IV every 12 hours.

That following morning, Pete was transferred to MSU-CVM Internal Medicine service for computed tomography and further work up. That morning, the following diagnostic

procedures were performed in order of completion: complete blood count, serum chemistry, urinalysis, and urine culture and sensitivity, computed tomography (CT) scan with contrast of his thorax, abdominal radiographs, and abdominal ultrasonography.

Diagnostic Approach/Considerations:

Complete blood count revealed a mild anemia indicated by a red cell count of 4.04 M/ul (4.30-8.77) and a hematocrit of 31.8% (34.0-60.0). A mild lymphopenia was also present [808 cells/uL (1200-6500)]. Serum chemistry indicated mild electrolyte disturbances including mild decreases in sodium [142.5 mmol/L (143-153)], calcium [7.8mg/dl (8.8-11.2)], magnesium [1.5 mg/dL (1.7-2.4)], moderate hypoalbuminemia of 1.7 g/dL (2.5-3.9), and a mild hypoproteinemia of 4.3 g/dL (5.5-8.0). Urinalysis was unremarkable, and urine culture produced no growth after 24 hours.

CT revealed contrast enhancing, soft tissue attenuating regions within the ventral aspect of the right cranial lung lobe, the lateral aspect of the caudal subsegment of the left cranial lung lobe, and the dorsal aspect of the right middle lung lobe. There was evidence of pulmonary fibrosis secondary to chronic inflammation, and the mediastinum was thickened and inflamed. There were multifocal, smoothly marginated, mineral attenuating foci within the parenchyma of multiple lung lobes. Pleural effusion was noted to cause retraction of the lung lobes and cranial displacement of the cardiac silhouette. The sternal lymph nodes and several cranial mediastinal lymph nodes were enlarged and homogenously contrast enhancing.

Radiographic findings were indicative of hepatomegaly. On ultrasound, a small amount of peritoneal effusion was observed. The liver was coarse in echotexture. The spleen contained multiple, poorly defined, hypoechoic nodules, and hepatic and renal lymph nodes were observed

to be enlarged and hypoechoic. Based on these results, it was unclear what was in Pete's thorax, but metastatic neoplasia was suspected. Surgical exploration of the thorax was recommended.

That afternoon, on February 22, Pete was anesthetized for a medium sternotomy. Upon exploration of the thorax, the mediastinum was severely thickened, pale yellow, and had a cobblestone texture. Similar pale, yellow nodules were adhered to the caudal thoracic wall and diaphragm. The sternal lymph nodes were subjectively large, and there was a one-centimeter nodule palpated within the right cranial lung lobe. Two sternal lymph nodes were removed along with the nodule from the right cranial lung lobe. Most of the mediastinal mass was debulked; however, portions of the mass were left, especially around structures such as the phrenic nerve and caudal vena cava. Based on the appearance and location of the mass, the primary differential diagnoses included neoplasia, or bacterial or fungal pyothorax. The mass, lymph nodes, and lung nodule were submitted for histopathology, and a swab of the mediastinum was taken for aerobic and anerobic culture. The results of the culture showed no growth after 24 hours and neither *Nocardia* nor *Actinomyces* were isolated. Biopsy samples of all tissues confirmed a diagnosis of high-grade histiocytic sarcoma.

Pathophysiology

Histiocytic sarcoma (HS) is an uncommon to rare malignant neoplasm of dendritic cell origin and rarely cells of the macrophage line.[2,3] This disease is known to be extraordinarily aggressive with a high metastatic rate.[4] Previously termed "malignant histiocytosis", histiocytic sarcoma is broken down into three subtypes: localized, disseminated, and hemophagocytic.[3] For purposes of this study, only localized and disseminated histiocytic sarcoma will be discussed. Localized histiocytic sarcoma (LHS) most often occurs as a solitary, aggressive mass, while

disseminated histiocytic sarcoma (DHS) has disseminated or multiorgan involvement; however, these two subtypes may be a continuum of the same disease at different stages.[1,3,4] Multiple predilection sites have been reported to include the subcutis, lung, liver, spleen, lymph nodes, joint space, bone marrow, central nervous center, nasal cavity, and mediastinum.[1,3,4]

HS is more common in dogs than cats and represents less than 1% of cancers of the lymphoreticular system.[3] A definitive cause remains unclear; however, genetic predispositions and chronic inflammation have been reported as risk factors for this disease.[3,5] There is no sex predilection, and any breed can develop HS, but predispositions to HS are reported in Bernese mountain dogs (BMD), Rottweilers, Flat-Coated Retrievers, Miniature Schnauzers, and Pembroke Welsh Corgis in Japan.[1,3,4,6] Presenting dogs are often middle aged to older; and BMDs are often diagnosed at a younger age with a more severe form of the disease.[3,7] Clinical signs and exam findings vary and are often related to extent of disease and the organ(s) of involvement.[3,4] If physical exam findings are indicative of multiple organ system involvement, DHS becomes more likely.[4]

Diagnosis can be obtained via cytological or histological examination; however, further workup should be performed to help differentiate LHS from DHS and for staging.[3] Minimum database should include a complete blood count, chemistry panel, urinalysis, thoracic radiographs, and abdominal radiographs and ultrasound.[1,3] Bone marrow biopsy and lymph node aspirates can be performed if necessary.[1] Complete blood count findings can include multiple cytopenias, most often a regenerative anemia, due to phagocytosis by macrophages.[1,3] Chemistry results usually vary, but findings can include elevated liver enzymes, hypocholesterolemia, hypoalbuminemia, hyperbilirubinemia, and rarely hypercalcemia.[1,3]

Thoracic radiographs may show pulmonary consolidation or nodules, pleural effusion, and diffuse interstitial pattern.[3,4] Radiographs of the abdomen can be vague, but commonly show hepatomegaly and splenomegaly.[4] On ultrasonography, hypoechoic nodules are commonly seen in the spleen and can sometimes be appreciated in other organs such liver, kidneys, and adrenal glands.[3,4] Hepatomegaly and mottling of the liver can be observed, and other findings can include lymphadenomegaly and abdominal effusion.[3,4] Advanced imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) may also be performed and may aid in determining anatomic origin and invasiveness of these tumors. For intrathoracic histiocytic sarcoma, pulmonary masses and intrathoracic lymphadenopathy were most commonly reported.[8] Masses in the right middle lung lobe are significantly more common, and the most common lymphadenopathies typically involve the sternal and tracheobronchial lymph nodes.[8] CT examination of these patients showed the majority of the masses being mild to moderately enhancing, heterogenous, poorly marginated, and bronchocentric.[8]

Fine-needle aspiration, and in rare cases evaluation of malignant effusion, can be done to obtain samples for cytological evaluation.[3] Cytology samples typically yield moderate numbers of single to small clusters of histiocytic cells that have marked anisokaryosis and anisocytosis, with cytoplasmic hemosiderin granules and vacuolation commonly seen.[3,4] Often times, immunocytochemistry is needed to help definitively confirm HS due to lack of differentiation and pleomorphism.[3] Histologically, examination of abnormal tissues often reveals sheets of pleomorphic population of atypical histiocytic cells and multi-nucleated giant cells, often with bizarre mitotic figures.[3,4] Immunohistochemistry can be performed using antibodies to CD18.[3] The CADET HM assay is an available test that looks for copy number aberrations consistent with those found in HS using either cytology or biopsy samples.[3] This test offers a 95%

specificity, and a 78% sensitivity.[3] Unfortunately, there are no immunohistochemical or histopathological differences in LHS and DHS, and differentiation should be based on staging, exam findings, and clinical presentation.[1,4]

Treatments and Prognosis

Histiocytic sarcoma has been shown to resemble other forms of neoplasms; therefore, a definitive diagnosis should be obtained prior to the initiation of treatment.[1] Differentiation of LHS and DHS should also be determined to assist in guiding therapy and informing owners of the expected prognosis.[3] For LHS, surgical removal/debulking may be appropriate followed by chemotherapy, whereas for DHS, only systemic chemotherapy is recommended.[1,3] Limited data is available in the efficacy of radiation for LHS and further investigation is warranted; however, dogs with HS of the joint receiving radiation had longer survival times than the dogs that did not receive it.[3] In one study involving a cat with thoracic HS, the use of thoracic omentalization was beneficial in reducing the amount of pleural effusion and reduced the overall need to regularly drain the thorax.[9]

Lomustine (CCNU) is accepted as the systemic chemotherapy of choice, as it has been shown to have the most activity against canine HS.[3,10,11] Doxorubicin has also been shown to be effective with combination of lomustine; however, further studies are needed to evaluate its use as a single agent against HS.[3,12] In a recent study, dasatinib was shown to have use as a potential single agent for the treatment of HS.[13] For cases that are unresponsive to lomustine and doxorubicin, dacarbazine, epirubicin, vinorelbine, paclitaxel, and metronomic lomustine and chlorambucil have been used as rescue agents, but further studies are needed.[1,3] It is reported that steroids should not be used in treatment of HS, as they have been associated with a negative

prognosis in multiple studies.[3,7] Novel therapies include the use of bisphosphonates allosteric SHP2 inhibitor SHP099.[3,14]

Prognosis for HS is relatively poor, and many dogs are euthanized at the time of diagnosis.[1] LHS has a more favorable prognosis with dogs having a median survival time around 398 days; however, LHS involving internal organs is reported to have a MST of 1 month from the time of diagnosis.[4,7] The MST for dogs with DHS is roughly 85-106 days and rapid clinical deterioration usually occurs.[4,7] Furthermore, certain factors were noted to be associated with a poorer prognosis including use of corticosteroids, anemia, hypoalbuminemia, thrombocytopenia, and evidence of giant cells on histology.[3,4] Overall, these tumors are aggressive and likely to metastasize; therefore, it important to do clinical staging to inform owner of the expected prognosis.[3,4]

Case Outcome

After Pete's median sternotomy was performed, he recovered uneventfully. In the days following, Pete was maintained in the ICU. His chest tube was drained every four hours, and the amount of pleural effusion drained decreased over the following two days after surgery; however, the amount of fluid drained steadily produced approximately 1.2 mls/kg/hr. On February 28, six days after surgery, Pete's biopsy results were obtained confirming the presence of histiocytic sarcoma. Due to the poor prognosis, Pete was euthanized and body was submitted for necropsy. Necropsy confirmed that Pete had mediastinal histiocytic sarcoma that was widely disseminated throughout the thoracic cavity and metastasized to both the liver and spleen.

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