Simon's in the Hot Zone

Julie Holdridge

Mississippi State University College of Veterinary Medicine

Class of 2019

Clinicopathologic Conference

December 14th, 2019

Advisor: Dr. John Thomason, DVM, MS, Diplomate ACVIM

Introduction:

Systemic fungal infections are a significant cause of disease for both dogs and cats in many regions of the United States[4]. Most fungal pathogens gain entry into the body through the respiratory tract and will disseminate to other body systems. Clinical signs are non-specific and include lethargy, anorexia, with possible respiratory or gastrointestinal involvement. Unfortunately, fungal infections can be difficult to diagnose in the earlier stages of disease. The most common systemic mycoses of dogs and cats includes blastomycosis, histoplasmosis, coccidiomycosis, and cryptococcosis. This case report will focus on histoplasmosis in the canine patient. Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum,* which is an organism most prevalent in moist soil containing bat or bird waste.

The greatest frequency of cases are reported along the Ohio and Mississippi river valleys, but have occurred in other regions of the country where fungal growth is favorable and in caves where birds or bats reside. Clinical signs are general and include fever, lymphadenopathy, dyspnea, cough, lethargy, and diarrhea[6]. Historically, obtaining a diagnosis relied on identifying the organisms on cytology or histopathology, but an ELISA based antigen detection is available as a non-invasive diagnostic test[6]. Treatment involves long term antifungal therapy, oxygen supplementation, and corticosteroids to control inflammation if indicated. Prognosis for cases that are localized to the lungs or gastrointestinal tract is good to excellent with appropriate therapy. For disseminated cases with multiple organ systems involved, the prognosis is more guarded as some experience a severe inflammatory response when the organisms die following initiation of antifungal therapy.

History and Presentation:

Simon is a 2 year old male intact Yorkshire terrier who presented to Mississippi State University College of Veterinary Medicine (MSU-CVM) Internal Medicine department on August 30th, 2018 for elevated liver enzymes and declining health status. Three weeks prior to Simon's presentation at MSU-CVM, his owners noticed him being lethargic with an increased respiratory rate and effort after minimal activity. He also had a decreased appetite, vomiting, and diarrhea. Simon is housed indoors, but goes outside for walks and to urinate and defecate. Simon is up to date on vaccines. His diet consists of Cesar wet dog food and he lives with three other dogs at home. His owners report that they took Simon and their other dogs to a nearby lake for a walk two weeks prior to the onset of his signs.

Simon was taken to the veterinarian on August 20th, 2018 for assessment of his anorexia, lethargy, exercise intolerance, vomiting, and diarrhea. He was hospitalized for two days on intravenous fluids and was sent home on Primor. One week later, Simon showed no signs of improvement and continued to be anorexic, lethargic, had bloody diarrhea, but was no longer vomiting; therefore, his owners brought him back to the veterinarian. At this time, a fecal float and giardia test were performed. Both test were negative and Simon was sent home with Metronidazole, Clavamox, and Ponazuril. Over the following three days, Simon's health status did not improve and he returned to the veterinarian. Simon had an intravenous catheter placed and was started on fluids. Bloodwork revealed the following abnormalities: thrombocytopenia, hyperphosphatemia, hypoalbuminemia, hyperglobulinemia, hypoglycemia, and elevated liver enzymes. Throughout the day while Simon was hospitalized, he became icteric and pale with an

increased respiratory effort. He was then referred to MSU-CVM Internal Medicine department for further workup.

On presentation to MSU-CVM Internal Medicine department, Simon was quiet but alert and responsive. He had an increased respiratory rate at 72 breaths per minute with an increased inspiratory effort. His pulse was 120 beats per minute and temperature was 103.7°F. Simon's peripheral pulses were fair, and his mucus membranes were pale icteric and tacky with a capillary refill time of two seconds. Simon was estimated to be about 5% dehydrated. He had decreased lung sounds ventrally and decreased heart sounds bilaterally. His liver was enlarged, but not painful on palpation. A thoracic fast scan revealed moderate pleural effusion and a scant amount of pericardial effusion. Abdominal fast scan revealed free fluid in all four quadrants. A thoracocentesis was performed and 249 milliliters of fluid was collectively removed from the left and right side of the thorax. A diagnostic abdominocentesis was performed and 3 milliliters of fluid was removed from the ventral abdomen. A sample of the thoracic and abdominal fluid was submitted for cytological evaluation. A CBC demonstrated a mild anemia, moderate neutrophilia, and mild monocytosis. A blood chemistry was performed and found Simon to have hyponatremia, hypochloremia, hypoglycemic, hypoalbuminemia, elevated alkaline phosphate and total bilirubin, and hyperglobulinemia. Thoracic radiographs revealed moderate pleural effusion, and a mild, diffuse, unstructured interstitial pulmonary lung pattern. Abdominal radiographs revealed a decrease in serosal detail and an enlarged liver.

Simon was maintained overnight on Hetastarch and a Plasmalyte constant rate infusion in the Intensive Care Unit. On August 31st, an abdominal ultrasound was performed and identified peritoneal effusion, hyperechoic mesentery, a diffusely hyperechoic liver, hyperechoic material

on the gravity dependent portion of the bladder, enlarged adrenal glands bilaterally, patchy regions of thickening of the stomach, diffusely corrugated duodenum, enlarged pancreas with irregular marginations, jejunal loss of normal wall layering, right and left inguinal, left and right medial iliac, and mesenteric lymph node enlargement. Fine needle aspirates were taken of the liver, mesentery, and right medial iliac lymph node.

Shortly after Simon's abdominal ultrasound, cytologic evaluation of the thoracic fluid previously submitted returned with a diagnosis. The fungal organism *Histoplasma capsulatum* was seen within many macrophages in the thoracic fluid. The organism was also identified on every aspirate taken, and on a blood smear. Simon was diagnosed with disseminated histoplasmosis.

Pathophysiology:

Histoplasmosis, a disease process that occurs primarily in dogs, cat, and humans, is caused by the fungal organism *Histoplasma Capsulatum*. The fungus lives in the soil of North and Central America and is endemic in the areas around the Ohio and Mississippi River Valleys. The primary reservoir of Histoplasma appears to be the bat, but many bird species have also been implicated because the organism can be found in the intestines and guano[5]. The organism grows best in nitrogen rich fecal material or soil in temperate or subtropical climate.

Infection of Histoplasma is established primarily by inhalation of the mycelial spores which are small enough to reach the lower airways. Oral exposure may also result in disease of the gastrointestinal system in some animals[1]. Once the spores are inhaled, the microconidia will convert to the yeast form in the small airways of the lower respiratory tract where reproduction

occurs by budding. The fungal organisms are then phagocytosed by the host alveolar macrophages in which further replication takes place. At this point in the disease process, the organism can either remain localized to the respiratory system, or become generalized by lymphatic and hematogenous dissemination. The most common sites to experience disseminated disease include the gastrointestinal tract, the lymph nodes, spleen, liver, and bone marrow[1]. Differential diagnosis with the typical presenting signs include other system mycotic infections, a protein-losing enteropathy, and severe intestinal disease (IBD, Gastrointestinal lymphoma). Infection with *Histoplasma* represents a defect in cell-mediated immunity of the host's defense system. The incubation period of Histoplasmosis may range from 2-3 weeks to years depending on the extent of the immune response of the host[1]. The organism load in infected tissues is typically high and will result in granulomatous inflammation.

Diagnosis of Histoplasmosis is suspected in patients with the presence of a miliary or nodular pattern on thoracic radiographs with history of exposure to an endemic region. Gastrointestinal signs, lymphadenopathy, and hepatomegaly further support the diagnosis, but confirmation requires cytologic or histopathologic examination of affected tissues. Bloodwork typically reveals a normocytic, normochromic, non-regenerative anemia with leukocyte parameters being variably affected. With gastrointestinal involvement, hypoalbuminemia is common as well as elevated liver enzymes, hyperglobulinemia, hyperbilirubinemia, and hypercalcemia. Definitive diagnosis is made upon fine-needle aspiration and cytologic evaluation of the organisms usually within phagocytic cells and appear as single to multiple round cell bodies with a basophilic center and clear, thin outer capsule[3]. Serologic testing for antibodies against Histoplasma is not recommended due to poor diagnostic sensitivity, however, an ELISA assay for *H. capsulatum* antigen can be used on urine or serum and has good

sensitivity and specificity, but may cross react with other fungal infections including blastomycosis[6].

Treatment and Management:

Treatment for histoplasmosis includes oral azole antifungal agents with itraconazole or fluconazole being the preferred options. In a retrospective case study of 61 dogs receiving treatment for *Histoplasma capsulatum*, there were no differences identified between antifungal agents (fluconazole and itraconazole) in survival, clinical remission, or disease relapse rates[1]. The selection of fluconazole over itraconazole may be made in cases with ocular or neurological involvement due to fluconazole's ability to cross the blood-aqueous, and blood-brain barriers, respectively. Side effects of itraconazole or fluconazole therapy include mild elevations of hepatic transaminase activity and cutaneous reactions consisting of ulcerative dermitits and vasculitis. Duration of treatment with azole medication is at least 4-6 months and can span up to a year or more. Cessation of therapy typically occurs one month after the patient has demonstrated resolution of all clinical signs, resolution of physical examination abnormalities, and resolution of radiographic evidence of disease[3]. A negative urine antigen test can also confirm remission of disease and aid in the discussion to discontinue azole therapy.

For cases with severe disseminated disease, or those refractory to azole therapy alone, Amphotericin B has been recommended for more rapid control of the fungal disease[3]. Due to the nephrotoxic effects of Amphotericin B, serial blood chemistries should be run to monitor kidney function as well as urine sediment evaluation for the presence of tubular casts. The use of corticosteroids for animals with histoplasmosis is controversial due to their impairment of cell-mediated immunity that is crucial for protection and can lead to worsening fungal infection[3]. However, much of the morbidity and mortality that accompanies the treatment of Histoplasma

results from massive inflammation that occurs as a response to the death of fungal organisms which is most profound in the first week of treatment. Animals with respiratory compromise from pulmonary fungal infection would benefit from an anti-inflammatory dose of corticosteroids either simultaneously at initiation of antifungal medication, or if respiratory signs have worsened over the first few days of azole therapy.

Once resolution of the disease has been achieved, relapse is uncommon, but if it does occur, azole therapy should be reinitiated. Owners should be educated about the mode of transmission of histoplasmosis because of the risk to human health. Histoplasmosis is not transferred from animal to animal, or animal to human, but rather through a common environmental source. Avoiding at risk or endemic areas is the best means of prevention as there is no vaccination available.

Case Outcome:

On August 31st, 2018 Simon's owners elected to humanely euthanize him. Simon's declining health status, guarded prognosis, cost of hospitalization, and lengthy antifungal therapy were all factors taken into consideration. The owners were informed about the route of transmission of *Histoplasma capsulatum.* Although Histoplasma cannot be transferred from mammal to mammal, it is possible that they or their other dogs at home could be infected from a common environmental source. It was recommended that a urine antigen test be performed on the other dogs in the household determine if they have become infected. The family was also advised to see their physician regarding any questions they may have about human infection. The location of Simon's family of Senatobia, Mississippi is in a highly endemic or "Hot Zone" for Histoplasmosis according to the Center for Disease Control's published map of "Areas Endemic for Histoplasmosis."

References:

1. Wilson, A. G., DVM, KuKanick, K. S., DVM, PhD, Hanzlicek, A. S., DVM, MS, & Payton, M. E., PhD. (january 15,2018). Clinical signs, treatment, and prognostic factors for dogs with histoplasmosis. *Journal of American Veterinary Medical Association, 252*(2), 201-209. Retrieved November 25, 2018.
2. Elad, D. (2018). Therapy of Non-Dermatophytic Mycoses in Animals. *Journal of Fungi, 4*(120), 2-16. doi:10.3390/jof4040120
3. Kerl, M. E., DVM. (2003). Update on canine and feline fungal diseases. *The Veterinary Clinics Small Animal Practice, 33*, 721-747. doi:10.1016/S0195-5616(03)00035-4
4. Salzer, H. J., Burchard, G., Cornely, O. A., Oliver, Lange, C., Rolling, T., & Schmiedel, S. (2018). Diagnosis and Management of Systemic Endemic Mycoses Causing Pulmonary Disease. *Respiration, 96*, 283-301. doi:10.1159/000489501
5. Diaz, J. H., MD, PhD. (2018). Environmental and Wilderness-Related Risk Factors for Histoplasmosis: More Than Bats in Caves. *Wilderness & Environmental Medicine, 29*(4), 531-540. Retrieved November 25, 2018.
6. Cunningham, L., DVM, DACVIM, Cook, A., BVM&S, DACVIM, DECVIM, Hanzlicek, A., MS, DVM, DACVIM, Harkin, K., DVM, DACVIM, Wheat, J., MD, & Goad, C., PhD. (2015). Sensitivity and Specificity of Histoplasma Antigen Detection by Enzyme Immunoassay. *Journal of American Animal Hospital Association, 51*, 306-310. doi:10.5326/JAAHA-MS-6202