Canine Histoplasmosis: A Case Report

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Class of 2018

Clinicopathologic Conference

Presented on April 6, 2018

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Introduction

Histoplasmosis is reportedly the most commonly diagnosed systemic mycosis in dogs (1, 2). The causative organism, *Histoplasma capsulatum*, is a thermally dimorphic fungus which thrives in nitrogen-rich organic material such as bird and bat feces (3 – 5). It has a worldwide distribution, but is particularly common in the Mississippi, Missouri, and Ohio River Valleys (6 - 8). The route of transmission is via inhalation of microconidia (2, 9), which transition to a unicellular yeast within the lungs. Within the lungs the yeast replicate via budding. Infection may be limited to the respiratory or gastrointestinal tract, or conversely, may be widely disseminated throughout the body (10, 11). Clinical signs are frequently nonspecific and may include lethargy, anorexia, weight loss, and fever. Gastrointestinal signs such as diarrhea, melena, tenesmus, and hematochezia are common in dogs. Respiratory signs may or may not be apparent (2, 7, 10). As such, in endemic regions, Histoplasmosis should be included as rule out for young outdoor dogs with ill thrift and gastrointestinal signs. The treatment of choice is a protracted course of itraconazole (10, 12) in combination with terbinafine. Prognosis is generally dependent on severity and chronicity of the disease in addition to the immune status of the host. Dogs with disseminated Histoplasmosis tend to have a poorer prognosis than those with disease confined to the gastrointestinal or pulmonary systems (10).

History

River, a 4 month old intact male Labrador Retriever, presented to the MSU-CVM Internal Medicine service on January 2, 2018 as an emergency referral for ascites, weight loss and abdominal distension. River was reported to be a happy and healthy puppy with a normal appetite until approximately 3 weeks prior to presentation, at which time his owners noted that River began losing weight and muscle mass in spite of a normal

appetite. Approximately 1 week later, River became inappetant and had both vomiting and regurgitation episodes. On December 29, 2017 his owners noted that River's abdomen had started to become distended, and River was evaluated by his primary veterinarian on December 30, 2017, where radiographs were performed and were reported to reveal metallic foreign bodies and ascites. Bloodwork at that time revealed a moderate anemia (hematocrit 22.99%) and severe hypoalbuminemia (1.4 g/dL). A sample of free fluid from River's abdomen was obtained and found to be a transudate. River was started on metronidazole and furosemide; however, he failed to improve. Repeat radiographs were taken by River's primary veterinarian prior to referral on January 2, 2018, which revealed persistent abdominal effusion, and the previously described metallic foreign bodies were no longer seen. River was then referred to the MSU-CVM. At the time of presentation, his owners reported that River had been increasingly lethargic, with a poor appetite, and continued watery diarrhea. At the time of presentation River was up to date on vaccinations and preventative medications.

Presentation and Diagnostics

Upon presentation River was quiet, but alert, and responsive. His vital parameters were within normal limits. A triage examination revealed moderate hypotentsion (systolic 80-90mmHg), a normal ECG and normal Sp02. Cardiothoracic auscultation was within normal limits, and he had peripheral lymphadenopathy. River's abdomen was markedly distended and was uncomfortable on abdominal palpation. An abdominal and thoracic FAST scan was performed and revealed no obvious free fluid, although complete evaluation of the retroperitoneal spaces was limited by the abdominal distension. River was started on intravenous fluids and he was monitored closely for any signs of third spacing. Blood was drawn for a CBC, serum chemistry, baseline cortisol and GI panel. Bloodwork revealed a moderate regenerative

anemia, moderate hypoalbuminemia, and mild thrombocytopenia. The snap parvovirus test was negative, and the baseline cortisol ruled out Addison's disease. A fecal examination was performed, and no ova or parasites were seen. All parameters on River's canine GI panel were within normal limits. Thoracic radiographs revealed a moderate to severe diffuse unstructured interstitial pattern and sternal lymph node enlargement. No esophageal abnormalities were noted. After further evaluation of abdominal radiographs performed by River's primary veterinarian, an abdominal ultrasound was performed that revealed hepatic and splenic enlargement, bile duct dilation, and enlarged hepatic and pancreatic lymph nodes.

Pathophysiology

When soilborne, *H. capsulatum* forms microconidia which are inhaled by the host. In the terminal bronchi, the fungus transitions to its yeast form (13). The unicellular yeast is subsequently phagocytized by alveolar macrophages where it replicates and ultimately destroys the host macrophage. In the absence of competent cell mediated immunity, yeast cells may further migrate to reticuloendothelial tissues such as the liver, spleen, and lymph nodes then further disseminate to the gastrointestinal tract, central nervous system, skin, eyes, or bones (14 - 16). The incubation period for histoplasmosis is widely variable, as some dogs may combat the initial infection and remain subclinically or latently infected until a period of immunosuppression permits reactivation of infection (7).

Clinical signs vary according to the organ system(s) affected. Signs may be non-specific; however, dogs often have gastrointestinal involvement (7). Commonly observed clinical signs in dogs with histoplasmosis include diarrhea, inappetance, weight loss, lethargy, pale mucous

membranes, and fever (15 - 17). In dogs with pulmonary manifestation of histoplasmosis, respiratory signs including coughing, dyspnea, and harsh or absent lung sounds may be noted (15, 18, 19). Clinical signs associated with the disseminated form may include lymphadenopathy, vomiting, ascites, icterus, hepatomegaly, skin lesions, uveitis, lameness due to bony involvement, and neurologic dysfunction (15, 18 – 23).

Diagnostic Approach / Considerations

Definitive diagnosis of *H. capsulatum* infection is made by identifying the organism in affected tissues using histopathology or cytology. Microscopically, *H. capsulatum* organisms may be seen extracellularly or within phagocytic cells. Organisms typically appear ovoid to spherical with a basophilic center surrounded by a clear halo and are 2 to 5 µm in diameter (7, 17, 23, 24).

Serological assays for detection of *H. capsulatum* antibody and antigen are available. A positive test for *H. capsulatum* antibody detection using complement fixation or gel immunodiffusion may indicate exposure to the pathogen, but not necessarily ongoing infection. Cross-reaction with *Blastomycoses spp.* is also possible. Due to their poor diagnostic sensitivity, serologic antibody tests have limited clinical applications as a negative test does not rule out *H. capsulatum* infection (7, 15, 25).

Conversely, testing for *H. capsulatum* via urine antigens is more reliable for Histoplasmosis detection. This ELISA detects a glycoprotein antigen that is released from *H. capsulatum* yeast and excreted in urine (26). As with serological antigen and antibody tests, cross

reactivity with *Blastomycoses spp.* and *Paracoccidioides spp.* is also possible with the urine antigen assay (2, 26).

Culture of *H. capsulatum* entails significant zoonotic risk and may require up to 6 weeks before positive identification may be made. Thus, fungal culture is a rarely indicated diagnostic modality for Histoplasmosis (7, 27, 28).

Ancillary tests such as diagnostic imaging and cytology are performed as part of the diagnostic approach to a patient with gastrointestinal signs. Thoracic radiographs may reveal a bronchial, alveolar, or classically, an interstitial "snowstorm" pulmonary pattern (15, 16, 29, 30). Other reported features of thoracic radiographs of dogs with Histoplasmosis include hilar, tracheobronchial, or sternal lymphadenopathy, lung consolidation, and pleural effusion (18, 29). Abdominal imaging may divulge enlargement of the liver, spleen, or kidneys, with or without peritoneal effusion (15, 16, 31). Intestinal thickening, mesenteric lymphadenopathy, and decreased hepatic echogenicity may also be noted (33). The most commonly observed hematological abnormality is a normocytic, normochromic, non-regenerative anemia (2, 7, 15, 16). Neutropenia or neutrophilia may be seen, and thrombocytopenia may be present in some severe cases (15, 16, 32, 33). Abnormalities on serum chemistry vary according to the organ system(s) affected; however, hypoalbuminemia is present is more than 75% of cases (7).

Treatment and Management Options

Antifungal drugs with activity against *H. capsulatum* include the azoles (ketoconazole, itraconazole and fluconazole). Ketoconazole is less effective and more likely to cause toxicity (34). Itraconazole is generally considered the azole drug of choice for canine Histoplasmosis. It

should be administered at a dose of 10 mg/kg orally every 12 to 24 hours (2, 10). The mechanism of action of itraconazole is inhibition of ergosterol synthesis via interaction with fungal cytochrome P450 enzymes. Itraconazole may also interact with mammalian cytochrome P450 causing hepatotoxicity (2). As such, it is recommended that liver values be monitored throughout itraconazole therapy. The course of treatment is often protracted. Itraconazole should be administered for a minimum of 4-6 months and may be required for greater than 24 months. The decision to stop treatment should be made based on resolution of lesions as well as serial urine antigen testing (2, 7). Development of resistance to fluconazole and voriconazole has been described in human medicine, but not with a newer azole medication called posaconazole. Posaconazole is being investigated for the treatment of Histoplasmosis in dogs (7).

Itraconazole is often combined with terbinafine for the treatment of canine fungal disease, this is because terbinafine acts at a different site in decreasing ergosterol synthesis. Terbinafine is a squalene epoxidase inhibitor and is generally well tolerated; however, GI upset, and hepatotoxicity are possible. Terbinafine should be prescribed at 30-35mg/kg PO q 12 hours.

Lipid-complexed amphotericin B should be used initially to treat dogs with severe acute pulmonary, disseminated or CNS disease. Nephrotoxicity is the biggest concern with these drugs and renal function monitoring is essential. This treatment should be followed by combined itraconazole-terbinafine therapy.

Other supportive treatments potentially include, oxygen therapy, blood transfusions, nutritional support, anti-emetics and liver supportive medications. Topical glucocorticoids and atropine may be required for patients with uveitis, and enucleation may be required to manage persistent ocular infection (7).

Unfortunately, for many pet owners itraconazole therapy may be cost prohibitive. Ketoconazole has been substituted in some cases; however, it is generally not as well tolerated as itraconazole and is less efficacious than itraconazole at clearing systemic mycotic infections (2, 15, 16, 35).

Case Outcome

Fine needle aspirates of River's liver, spleen, and peripheral lymph nodes were taken and revealed the presence of *H. capsulatum* organisms. Anti-fungal therapy with itraconazole and terbinafine was started on January 3, 2018. River was monitored closely in the ICU for any signs of adverse reactions related to the acute death of a large number of fungal organisms following initiation of treatment. While hospitalized, River was also treated with intravenous fluid therapy, and gastroprotectant medications. River was discharged on January 4, 2018 with itraconazole, terbinafine, and ondansetron.

River's initial *H. capsulatum* urine antigen, assessed on January 3, 2018 was 11.88 ng/mL. Repeat antigen testing was performed on January 24, 2018 (three weeks after initiation of anti-fungal therapy) yielded an antigen level of 7.39 ng/ml.

One week following discharge, one month following discharge, and every other month thereafter, River has returned to MSU-CVM for rechecks. At each appointment, repeat abdominal ultrasounds were performed which revealed resolving hepatosplenomegaly and reducing bile duct dilation. Repeat bloodwork has revealed consistent improvement in the previously noted anemia, hypoalbuminemia, and thrombocytopenia.

River's owners report that he is doing very well at home. He is tolerating antifungal therapy with minimal side effects (intermittent diarrhea) and his appetite has improved greatly. His abdomen is no longer distended and cranial organomegaly is no longer present. He is consistently gaining weight and is growing appropriately for a puppy of his age. He is bright and happy and has the energy levels of a normal puppy.

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