Histoplasmosis: Recognition, Diagnosis, and Treatment
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Epidemiology and pathogenesis

*Histoplasma capsulatum* is a saprophytic dimorphic fungus commonly found in the Missouri, Mississippi, and Ohio River valleys. In soil, it exists in a mycelial form; however when exposed to mammalian body temperatures, usually by inhalation, the fungus converts into a yeast. Yeasts survive intracellularly within monocytes and travel from the lungs to other organs of the body leading to dissemination of the organism and systemic histoplasmosis.

Clinical presentation

Histoplasmosis affects mostly young to middle-aged dogs who have outdoor exposure. Histoplasmosis can affect any age cat. Cats who spend their time strictly indoors can also become infected; in one study approximately one-third of affected cats were considered by their owners to live strictly indoors. Presenting complaints most commonly include inappetence, weight loss, vomiting, fever, respiratory problems, large bowel diarrhea, and ocular disease, although other signs can also occur. On physical examination, pale or icteric mucous membranes, lymphadenomegaly, ocular changes (uveitis, retinal granulomas, etc.), increased respiratory rate and effort, hepatomegaly, splenomegaly, thickened intestines, and fever may all be appreciated.

Diagnosis

The most definitive method for diagnosing histoplasmosis in dogs and cats is by identification of the fungal organism by cytology or histopathology. The organism appears as a small (2-4μm diameter) yeast with a thin clear rim. Organisms are usually found intracellularly in multiples but occasionally exist as singlets and extracellularly. In some cases with bone marrow involvement, *Histoplasma* organisms can be seen in circulating monocytes on a CBC. Otherwise, a CBC may show a nonregenerative anemia, variable white count, and variable platelet count (may be low). Patients with histoplasmosis may have hypoalbuminemia, hyperglobulinemia, hypercalcemia, elevated liver enzyme activities, and hyperbilirubinemia. Chest radiographs frequently document a military or unstructured nodule interstitial pattern. As mentioned above, the most accurate diagnostic test is an aspirate or biopsy to document presence of the organisms. Affected organs with lower risk for sample collection, such as lymph nodes, skin lesions, and rectal scrape, should be sampled first. If a definitive diagnosis is not obtained with these tests, samples can be collected by aspiration from other affected organs such as liver, spleen, lung, and marrow, followed by more invasive tests as needed, such as intestinal biopsy.

For patients where cytology/histopathology are not able to provide a diagnosis or collection of these samples is considered unsafe, other diagnostic options exist. Serologic testing is available by various methods, but little research is available regarding the utility of this test for clinical veterinary patients with histoplasmosis and there has been concern regarding false negative results. Antigen testing has received much research attention recently and has become a helpful addition to our diagnostic options for patients with suspected histoplasmosis. A preliminary study using a third generation enzyme-linked immunosorbent assay (ELISA) for detection of *Histoplasma* antigen (MiraVista; Indianapolis, IN) identified *Histoplasma* antigen in 17/18 cats with histoplasmosis confirmed by either cytology or histopathology, resulting in a sensitivity of 94.4%. The same test was found to have 100% specificity based on 20 cats who had diagnostic workups including cytology, histopathology, or necropsy to confirm non-histoplasmosis illness. Research is ongoing to investigate the utility of this test with dogs, as well as the utility for using this test to guide decisions about length of treatment and relapses of fungal disease. Fungal culture is also an available diagnostic tool, but prolonged turnaround times to obtain results have made its use less practical for clinical veterinary cases.

Treatment

Little research exists regarding the optimal treatment drug choice and dosing protocols for histoplasmosis in dogs and cats. Traditionally, itraconazole has been considered the oral treatment of choice for histoplasmosis in dogs and cats, with dosing recommendations ranging from 5mg/kg PO BID for cats (Hodges) to 10mg/kg PO q 12-24h for dogs or cats (Bromel). Generic itraconazole is considered to be an acceptable option to brand name (Sporonox©), but compounded itraconazole should be avoided. Fluconazole is also commonly used and is especially helpful in cases with ocular or CNS involvement. Further research is warranted to determine the optimal dose for efficacy and safety of fluconazole in dogs and cats; current dose recommendations range from 2.5-5mg/kg PO q 12-24h (Bromel) to 10mg/kg PO BID (Reinhart), the latter being currently used at the author’s institution. Treatment should extend at least 2 months past resolution of all clinical signs, laboratory abnormalities, and radiographic changes, with most patients requiring therapy for at least 6 months. Relapses are somewhat common and owners should be educated to watch for recurrent signs. During therapy, patients are monitored closely (usually monthly) for adverse effects to theazole therapy (hepatotoxicity, altered...
appetite) as well as improvement or worsening of disease. Amphotericin B can be used in patients with fulminant disease or those who cannot absorb oral medications due to severe intestinal histoplasmosis. Additional medications including terbinafine, voriconazole, and others can also be considered for those patients not responding or having adverse effects to the above medications.

Select references