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Histoplasmosis

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Abstract: *Histoplasmosis is the most commonly diagnosed major systemic mycosis in dogs and the second most commonly reported fungal infection in cats. The causative organism,* Histoplasma capsulatum, *is endemic in 31 of the 48 contiguous US states and has a worldwide distribution.* Histoplasma *organisms enter the body via inhalation or, possibly, ingestion. They are phagocytized by macrophages and can be disseminated via the bloodstream or lymphatic system to the reticuloendothelial and gastrointestinal (GI) systems and, sometimes, the bones, skin, eyes, or brain. Clinical signs are often nonspecific, including lethargy, weight loss, and inappetence, although respiratory or GI signs may help localize the infection. Definitive diagnosis requires identification of* H. capsulatum *on cytology or histopathology. However, antigen testing may be useful in animals in the future. Itraconazole is the treatment of choice. The prognosis is fair for animals with pulmonary histoplasmosis and guarded to poor for those with GI or disseminated disease.*

Causative Agent and Pathogenesis

Histoplasmosis has a worldwide distribution, with cases reported in Canada,[1,2] Australia,[3] Japan,[4,5] Brazil,[6] Costa Rica,[7] the Panama Canal Zone,[8] and Turkey.[9] In North America, the disease is well known in the Mississippi, Ohio, and Missouri River valleys and is endemic in 31 of the 48 contiguous states.[10] Based on histoplasmin skin test results, the causative organism, *Histoplasma capsulatum*, is highly prevalent in the central part of the United States.[10] *H. capsulatum* naturally lives in soil containing nitrogen-rich organic matter (such as bird and bat excrement), where conditions accelerate sporulation.[7,11–13] The species exists as three distinct varieties: (1) var. *capsulatum* (a New World pathogen), (2) var. *farciminosum* (an Old World pathogen), and (3) var. *duboisii* (an African pathogen). All varieties are potentially pathogenic in humans and animals.[14,15] *H. capsulatum* was first reported as a pathogen in humans in 1906,[16] in a dog in 1939,[8] and in a cat in 1949.[9] In a number of large retrospective veterinary review articles, histoplasmosis was the most commonly diagnosed major systemic mycosis in dogs[17] and the second most commonly reported fungal infection in cats (after cryptococcosis).[18]

H. capsulatum is a thermally dimorphic fungus, existing in a mycelial form in the environment and as a yeast form in the host's body.[19] The saprophytic mycelial form produces two forms of spores, macroconidia and microconidia, which enter the body by inhalation or, possibly, ingestion.[20] Once in the lungs, the spores germinate and convert to the yeast form. Pulmonary macrophages phagocytize the fungal bodies, which then replicate intracellularly.[21] Replication may be terminated by the development of cell-mediated immunity.[21] Otherwise, organisms disseminate via the bloodstream or lymphatics[21] to the reticuloendothelial (liver, spleen, lymph nodes, and bone marrow) or gastrointestinal (GI) system or, sometimes, the bones, skin, eyes, or brain.[19,22–24]

Signalment and Risk Factors

Two studies[17,25] have identified at-risk populations in dogs. In one study of 238 dogs,[17] animals between the ages of 2 and 7 years (mean age, 3.6 years) were at increased risk for histoplasmosis. Likewise, in the other study,[25] most affected dogs were younger than 3 years. In both studies, male and female dogs appeared equally susceptible to infection.[17,25] *Histoplasma* infections were noted in dogs in the sporting, working, and terrier groups in one study[17]; the authors specifically identified pointers, Weimaraners, and Brittany spaniels as at-risk breeds. In the other study,[25] 58% of dogs were sporting or hound breeds, with the greatest prevalence in English pointers and coonhounds. This pattern of risk—young, outdoor animals and large working or sporting breed dogs—is common with infectious disease in veterinary medicine. A seasonal incidence of disease was suggested by one of the studies,[17] in which cases appeared to be clustered in the spring (February to April) and fall (September to November).

Studies of histoplasmosis in cats have shown incidences that roughly parallel those seen in dogs. In one study,[26] 13 (72.2%) of 18 affected cats were 3 years of age or younger. In a separate study of 56 cats,[18] the mean age of affected animals was 3.9 years, and Persians were marginally overrepresented. Male and female cats appear equally affected,[18] although smaller case series sometimes had more female cats than males.[26,27] Cats housed strictly indoors remain at risk for histoplasmosis.[28,29] Household dust or contaminated soil of potted plants has been postulated as a source of infection for these cats.[30]

Immune system function plays a role in any animal or person's susceptibility to *Histoplasma* infection. Immunosuppressive therapy with glucocorticoids has been associated with severe *Histoplasma* fungemia and death in some dogs.[23,31,32] Of six dogs that received immunosuppressive doses of prednisone, prednisolone, or dexamethasone for 3 to 14 days before histoplasmosis was diagnosed, all six died within a month of starting glucocorticoids, and four had severe *Histoplasma* fungemia before death.[23,31,32] In humans, histoplasmosis is associated with HIV infection and other immunosuppressive conditions.[11] A definitive link between feline retrovirus infection and *Histoplasma* infection has not been proven. Most *Histoplasma*-infected cats reported in the literature are FeLV negative.[28,33–38] However, cats with *Histoplasma* infection are occasionally retrovirus positive.[24,39] In one such case, an FeLV-positive cat was diagnosed with histoplasmosis while receiving long-term prednisone therapy for feline asthma and eosinophilic indolent ulcers.[39] In another case, an FeLV-positive cat with lymphoma was subsequently diagnosed with concurrent histoplasmosis.[40] Cats with histoplasmosis should be tested for feline retroviruses because retrovirus-associated immunosuppression may affect prognosis.[41]

Clinical Findings

Histoplasmosis has a reported incubation period of 12 to 16 days[42] but can be acute or chronic.[23] In one canine study,[22] the duration of clinical signs from onset to presentation ranged from just hours to more than 1 year. In comparison, duration of illness in cats before therapy ranged from 8 to 11 weeks in one study[27] and 2 to 12 weeks in another.[18] Most cats were brought for veterinary care within 4 weeks,[24] whereas 83% of dogs (20 of 24 cases) were admitted within 14 weeks of the first detectable clinical abnormality.[22]

Large surveys of animal populations document the identification of asymptomatic *Histoplasma* infection in dogs and cats during necropsy when organisms were isolated by culture.[43–45] This "benign" form of histoplasmosis may go unrecognized unless pulmonary lesions are incidentally detected on radiographs or a necropsy is performed.[46] In addition, apparent recovery from presumed pulmonary histoplasmosis without antifungal therapy has also been reported in four dogs.[42,47] These dogs had respiratory signs, including coughing and dyspnea, with characteristic radiographic changes and positive *Histoplasma* titers. The owners did not pursue therapy because of the guarded to poor prognosis; however, the dogs recovered at home and lived for years with no antifungal therapy.[42,47] Histoplasmosis may be recognized in isolated body systems (e.g., respiratory or GI) or as a multisystem, disseminated disease in cats and dogs.[48]

In cats and dogs, histoplasmosis can cause lesions in nearly all body systems, but the most common signs are referable to the respiratory, lymphatic, and digestive systems.[43] Clinical signs may be nonspecific and include lethargy or weakness, emaciation, dehydration, fever, and anorexia.[2,22,23,31,32,47,49–53]

Dogs

GI signs are common in dogs and may occur without detectable pulmonary signs.[22,52] The most common GI sign is large bowel diarrhea with hematochezia, mucus, and tenesmus.[23,30,51,52] When *H. capsulatum* infiltrates the small intestine, it causes large quantities of watery stool and may result in protein-losing enteropathy and weight loss.[30,51,54] Even in dogs with disseminated disease, the most common signs are diarrhea, hematochezia or melena, and weight loss. In endemic areas, histoplasmosis should be considered as a potential cause of chronic diarrhea and ill thrift. In one study, 18 of 24 dogs (75%) had a history and/or clinical signs referable to the GI tract.[22]

Although intestinal involvement is common, respiratory disease is also a classic feature of histoplasmosis in dogs. Respiratory signs often include coughing, dyspnea, harsh lung sounds, muffled heart and/or lung sounds, and ocular discharge.[22,23,43,47,49,50,53,55,56] Lesions may involve the pulmonary parenchyma, pleural space, or tracheobronchial lymph nodes. Pyothorax characterized by septic exudate containing intracellular *Histoplasma* organisms may be present. Compression of the mainstem bronchi from enlarged tracheobronchial lymph nodes often causes severe respiratory clinical signs.[47,57] Lymphadenopathy may be confined to the tracheobronchial area, generalized, or regional and peripheral.[2,22,23,31,32,50,56,58–61]

In dogs with disseminated histoplasmosis, major abdominal involvement may be indicated by vomiting,[43,56,62,63] ascites,[22,50–52,64] hepatomegaly,[22,32,50,51,53,56] and icterus.[22,32,51] Some dogs have musculoskeletal signs (lameness, swollen joints, and pain on palpation of the bones).[2,58–62] Infiltration of organisms into the bone marrow may result in anemia and pale mucous membranes.[22,23,50,53,60] Ocular signs include anterior uveitis, chorioretinitis, retinal detachment, and optic neuritis.[31,61,65,66] Central nervous system (CNS) signs relate to the specific location of lesions within the brain or spinal cord and include seizures, ataxia, depressed mentation, head tilt, nystagmus, strabismus, facial paralysis, and tetraparesis.[65–67] Skin lesions, which are uncommon, may be papules, nodules, ulcers, or draining tracts. Draining fluid may be serosanguineous or purulent.[3,63,68–70] Oral lesions (erosions and raised lesions on the tongue) have also been reported.[59,63]

FIGURE 1

Conjunctival hyperemia, corneoscleral inflammatory nodules, corneal edema and vascularization, and anterior uveitis with severe nodular iritis are evident in this cat with ocular histoplasmosis. Courtesy of Dr. Ian Herring, Virginia Tech

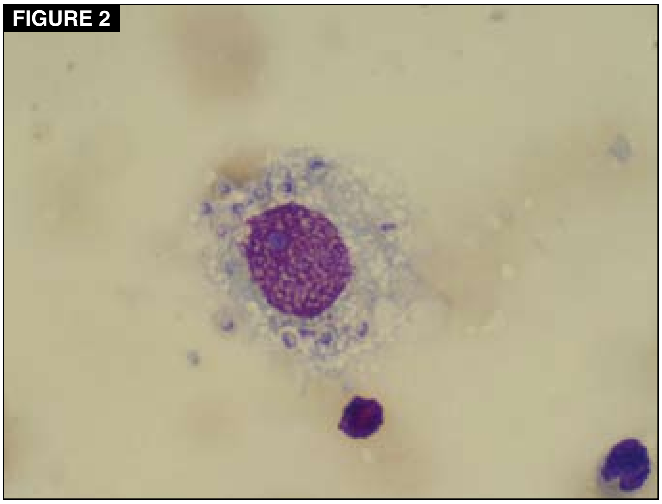
Cats

In contrast to dogs, cats generally have signs of respiratory or disseminated disease.[71] In a review of 96 cats, most clinical signs (67%) were nonspecific; respiratory, ocular, and musculoskeletal signs were also reported.[18] Anorexia and weight loss are reported as predominant or common clinical signs.[9,24,27,33–35,37,41,66,72–76]

In feline pulmonary histoplasmosis, dyspnea and tachypnea are common clinical signs, whereas coughing may be only occasional.[18,37] Coughing in dogs is sometimes due to compression of the mainstem bronchi from enlarged tracheobronchial lymph nodes, a feature of histoplasmosis that does not appear to be common in cats.[26] Cats with significant pulmonary radiographic changes sometimes do not exhibit any respiratory signs, despite apparently severe lung involvement.[77]

Disseminated feline histoplasmosis has numerous parallels to the disease seen in dogs. GI signs, including vomiting and diarrhea, have occasionally been reported.[27,36,39] Involvement of multiple organ systems may result in pale mucous membranes,[24,27,33,34,37,72,77] generalized lymphadenopathy,[24,40,73,74,77] and hepatosplenomegaly.[24,34] Chorioretinitis, optic neuritis, anterior uveitis, and retinal detachment[18] (**FIGURE 1**) have been reported. Fundic lesions have been described as slightly raised with a mottled, cobblestone tapetal layer.[66] Osseous involvement without demonstrated involvement of other organ systems has been reported in cats.[38] Musculoskeletal signs include lameness, swollen joints, and pain on palpation of the bones.[18] A case report described paraparesis leading to paraplegia and loss of deep pain in a cat with an extradural granuloma in the thoracolumbar area.[78] Skin lesions have been reported, including subcutaneous nodules[24,27,77] and ulcerative lesions.[28,29,66]

FIGURE 2



Macrophage with multiple phagocytized *Histoplasma* organisms from an endotracheal lavage sample in a cat with pulmonary disease.

Diagnosis

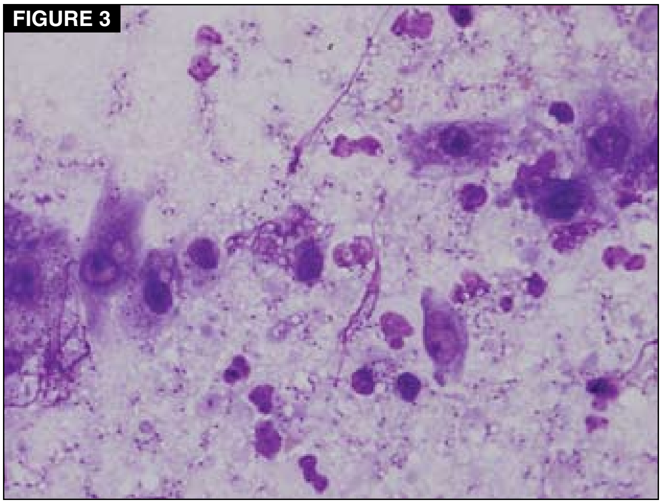
Cytology

A definitive diagnosis can be made by identifying *H. capsulatum* in cytology or histopathology samples. Different stains have been used for cytology, including Diff-Quik,[34,37] Wright,[50,56] and Giemsa.[79] Yeast cells are often seen within macrophages[5,23,24,27,32,52,74,77] or sometimes free.[2,28,74,75] Organisms are 2 to 5 μm in diameter with an oval to spherical, lightly basophilic center surrounded by a clear halo.[2–5,37,53,56,63,77] Rod-shaped organisms indicating a narrow-based budding may be seen in the cytoplasm of macrophages.[3,4] Organisms may be noted within mononuclear cells.[38] Cytology may identify *H. capsulatum* in numerous tissues corresponding to the clinical signs.

In animals with primarily GI involvement, organisms may be seen in rectal scraping specimens.[22] Rectal scraping is performed in awake or sedated animals by using a blunt instrument, such as a gloved finger or small curette, to scrape the superficial mucosa of the rectum. The goal is to obtain a sample that contains mucosal epithelial and inflammatory cells for cytology.[80] Rectal scrape cytology should not be confused with fecal cytology. In some cases, rectal scraping is negative, yet organisms are found on endoscopic or surgical biopsy of the intestinal tract. In cases of chronic large bowel diarrhea, colonoscopy may be particularly helpful in establishing the diagnosis. In numerous instances, necropsy has detected infiltrative *Histoplasma* organisms in the small and large intestines.

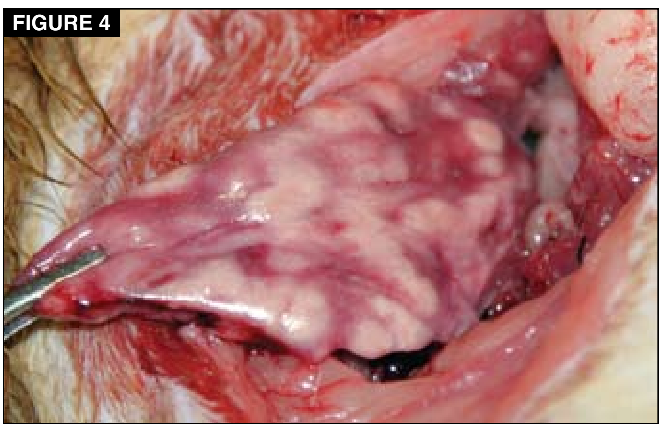
In cases with primarily respiratory involvement, organisms have been identified in pleural fluid,[34,50,53,56] transtracheal

FIGURE 3



Numerous extracellular and intracellular *Histoplasma* organisms from a fine-needle aspirate sample of lung tissue in a cat with pulmonary disease. Courtesy of Dr. Stephen Gaunt, Louisiana State University

FIGURE 4

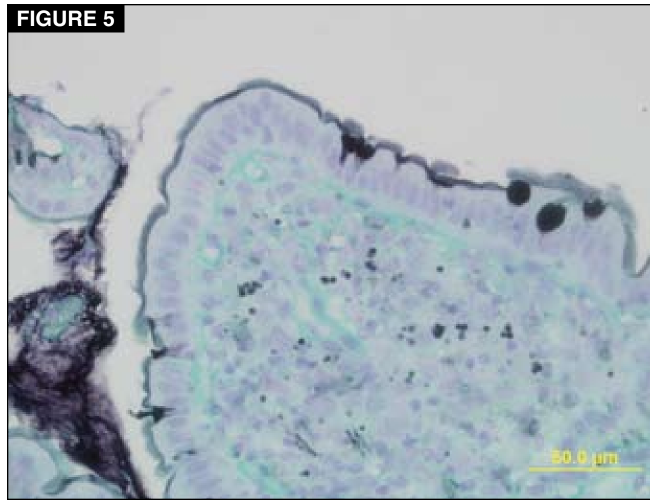


Gross necropsy of a cat with severe pulmonary histoplasmosis. Diffuse pale tan nodules were noted through the lung parenchyma.

washes[24,27,33,65,76] (**FIGURE 2**), bronchial washes,[81] bronchoalveolar lavage samples,[27,82] tracheobronchial brushings,[27] and lung aspirates[27,34,39,76,83] (**FIGURE 3**). Transtracheal wash or bronchoalveolar lavage may reveal mixed inflammation of macrophages and neutrophils, which can be nondegenerate or degenerate.[28,65] In chronic respiratory histoplasmosis, organisms may be sequestered within lymph nodes or granulomas and may be difficult to obtain for cytologic examination. In these instances, samples of airway secretions may not yield organisms, and lymph node aspiration or lung aspirate may be more productive. Histology and culture are sometimes necessary for confirmation.

In some cases of disseminated histoplasmosis, circulating organisms can be seen in peripheral blood smears, especially along the feathered edge,[39,60] and in buffy coat smears.[34,37,50] Organisms have been detected within monocytes,[22–24,31,32,37,49,52,60] neutrophils,[23,24,31,32,37,52,53] and eosinophils.[23,31] Bone marrow aspirate cytology may be diagnostic.[18] In a report of deep mycotic infections in cats, 16 of 56 animals with histoplasmosis had neutropenia, anemia, and/or thrombocytopenia on their complete blood count (CBC). *Histoplasma* organisms were present in the bone marrow cytology of 14 (88%) of these 16 animals.[18] Marrow cytology is variable but is characterized by hypercellularity, normal to decreased megakaryopoiesis, and decreased erythropoiesis with large numbers of macrophages, plasma cells, and lymphocytes.[23,24,27,37,60] Granulopoiesis may be decreased, normal, or increased.[23,24,27,37,60]

FIGURE 5



Gomori methenamine silver–stained section of colon tissue in a dog with colonic histoplasmosis.

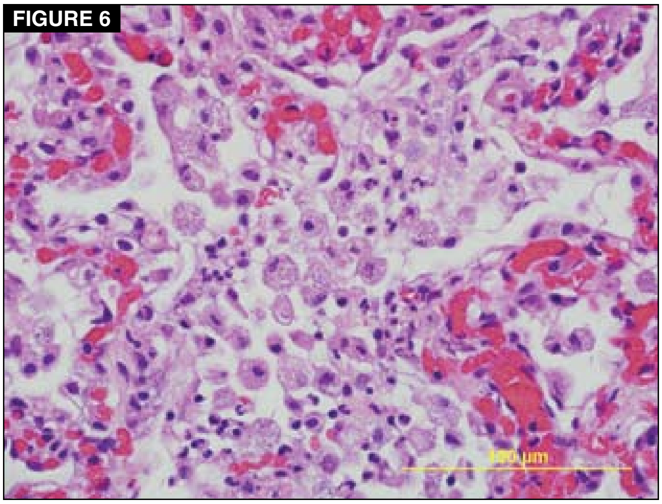
In cases of disseminated histoplasmosis, organisms may be detected in cytology samples from the liver,[24,34] spleen,[27] lymph node,[24,27,72,74,75,77] and skin.[27,28,66,77] In addition, *H. capsulatum* has been isolated antemortem from peritoneal fluid,[34,50,56] joint fluid,[38,77] and cerebrospinal fluid (CSF) samples.[65] In one such case, cytology of joint fluid identified intracellular organisms within nondegenerate neutrophils and mononuclear cells.[77] In a report of histoplasmosis involving the CNS,[67] CSF analysis detected mononuclear pleocytosis, occasional neutrophils, and elevated protein; organisms were later confirmed via necropsy.

Histopathology

Grossly visible findings on necropsy or at surgery include peritoneal effusion,[36,43,51,52] hepatomegaly,[23,43] splenomegaly,[23,48,77] enlarged mesenteric lymph nodes,[23,43,52] thickened intestines,[23,43,52] and enlarged tracheobronchial lymph nodes.[47] Surfaces of abdominal organs may have a granular appearance.[2] Additionally, gray, white, or yellow nodules have been noted on the serosal surface of the small intestine,[50,52] large intestine,[36,50] lungs[23,43,47,77] (**FIGURE 4**), liver,[52] adrenal gland,[52] and lymph nodes.[73,77]

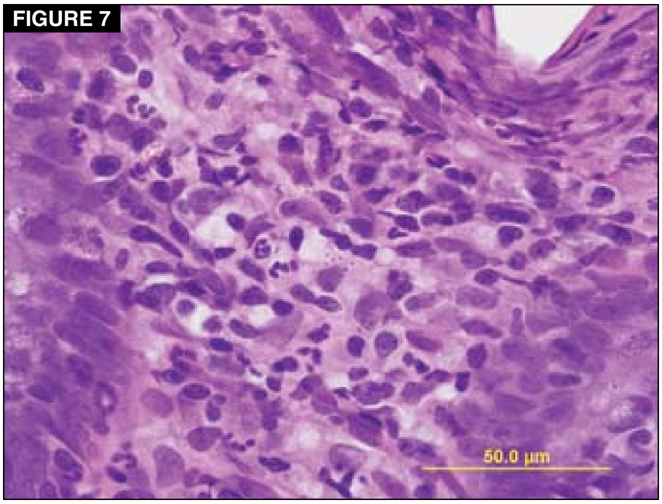
Histopathologic evaluation of infected tissues revealed granulomatous[24,77] to pyogranulomatous[2,3,67,83,84] inflamma-

FIGURE 6



Hematoxylin-eosin–stained section of lung tissue from a cat with severe pulmonary histoplasmosis.

FIGURE 7



Hematoxylin-eosin–stained section of colon tissue from a dog with colonic histoplasmosis.

tion. Organisms in tissue sections may be difficult to demonstrate with routine hemotoxylin–eosin stains, so special stains that stain the cell wall are often used, including Gomori methenamine silver, periodic acid-Schiff,[45,61,63,79] and Gridley fungal stain.[4,46] With these stains, the organisms appear as empty red or black rings[46] (**FIGURE 5**). In numerous studies involving surgical and necropsy specimens, disease could be identified in a wide variety of organs, including the lungs[22–24,29,74,77] (**FIGURE 6**), liver,[22–24,27,29,52,74,77] spleen,[22–24,27,29,52,74,77] lymph nodes,[22–24,27,29,52,74,77] bone marrow,[22–24,29] intestines[22,24,29] (small[23,52,77] and large[23,52]; **FIGURE 7**), kidneys,[23,24,29,74] adrenal glands,[23,24,29,52,64,74] brain,[22,24,74,77] spinal cord,[78] eye,[24,27,74,77] tongue,[59,63] cutaneous nodules,[27,77] bone,[74] and conjunctiva.[27]

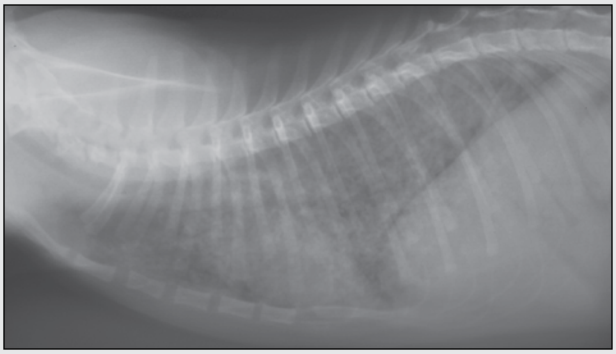
Immunostaining with polyclonal anti-*Mycobacterium bovis* IgG antibodies was evaluated as a single screening method for the histologic identification of microorganisms in skin biopsy specimens from various species, including dogs and cats. This technique was able to detect *Histoplasma* organisms and most other fungal and bacterial organisms in paraffin-embedded specimens.[85]

Radiography and Ultrasonography

Different radiographic lung patterns are associated with histoplasmosis, including bronchial,[22,75] interstitial,[22,24,25,47,60,61,75] and alveolar.[22,24–26,49,53,76] Interstitial patterns include linear,[26,33] nodular,[24,26,33,39,61,66,76,83] and miliary[24,33,34,56,61,83] patterns (**FIGURE 8**). Tracheobronchial lymphadenopathy or hilar lymphadenopathy with compression of the mainstem bronchi is noted in some dogs.[25,47,50,57,61] Pleural effusion,[50,53,56] sternal lymphadenopathy,[50] consolidated lung,[34,56] and a mass just cranial to the heart[55] have also been reported. The terms “snowstorm effect” and “cotton tuft” have been used to describe the radiographic lung pattern seen in many cases of histoplasmosis.[29]

FIGURE 8

Diffuse miliary pattern on thoracic radiographs of a cat with pulmonary histoplasmosis.



Lateral view.

Ventrodorsal view.

Different thoracic radiographic patterns may suggest different stages in the pathogenesis of pulmonary histoplasmosis. An interstitial pattern is presumably due to edema and interstitial inflammation. Short, linear, and small nodular densities are caused by the summation effect of large numbers of inflammatory cells and exudate. An alveolar pattern is due to flooding of the interstitium and alveoli with organisms and inflammatory cells. Tracheobronchial lymphadenopathy is seen as a discrete water–tissue density mass dorsal to the tracheal bifurcation. Narrowing of the mainstem bronchi occurs secondary to enlargement of these lymph nodes. Multiple calcified interstitial nodules and calcification of tracheobronchial lymph nodes may represent inactive disease. In a study of 29 animals with active pulmonary histoplasmosis (27 dogs and two cats),[25] 42% had tracheobronchial lymphadenopathy with interstitial pattern, 24% had tracheobronchial lymphadenopathy with minimal interstitial pattern, 24% (including one cat) had an interstitial pattern, and 10% (including one cat) had an alveolar pattern. In the same study, of eight animals that had inactive pulmonary histoplasmosis, defined as multiple calcified nodules with or without tracheobronchial lymph node calcifications, all were dogs. In a retrospective study of 18 cats with pulmonary histoplasmosis,[26] most cats had an interstitial pattern. This pattern was fine, diffuse, or linear in eight cats (44.4%) and nodular in eight cats (44.4%). Alveolar pattern was an uncommon finding (two cats; 11.2%). Tracheobronchial lymphadenopathy and calcified pulmonary lesions or lymph nodes were not noted.

Abdominal radiographs may reveal hepatomegaly,[22,32,33,34,47,49,50,53,60,77] splenomegaly,[22,32,49,50,60] renomegaly,[32,49] and peritoneal effusion.[47,49,50,52,53] Animals with signs of musculoskeletal disease may have radiographic changes in the extremities, including periosteal new bone formation,[58,60–62,74] osteolysis,[27,38,40,60–62,73–75,77] soft tissue swelling,[38,40,61,62,77] joint effusion,[61] and pathologic fractures.[74,75] Multiple bones are often involved. Bones below the elbow and stifle, especially the carpus and tarsus and immediately adjacent bones, are most frequently affected. The metaphyseal regions of long bones are often affected, suggesting hematogenous dissemination.[74]

Abdominal ultrasonography findings depend on the organs involved. In the GI form of histoplasmosis, ultrasonography may detect focal, mass-like diffuse thickening of the intestines. This type of thickening may be difficult to differentiate from neoplasia on the basis of wall measurements and symmetry.[86] Mesenteric lymph nodes may be enlarged, and effusion may be detected. Animals with liver involvement may have a large hypoechoic liver and ascites.[56]

Endoscopy

Colonoscopy may reveal increased mucosal granularity, friability, ulceration, and thickness.[87] Compression of mainstem bronchi can be assessed with bronchoscopy.[57]

Laboratory Data

Clinical pathology data vary depending on the manifestations of disease. The most common abnormality on the CBC is nonregenerative anemia.[22–24,27,32,37,50–53,60,65,67,72–75] Other hematologic abnormalities reported include leukocytosis with neutrophilia,[22,23,27,29,37,39,47,53,74] a left shift,[31,32,39,38,50,52,53] toxic changes in neutrophils,[31,37] neutropenia,[18,23,24,50,72,88] and thrombocytopenia.[18,23,24,27,32,37,38,50,53,60,65] Eosinophilia and basophilia were noted in a dog.[31] Pancytopenia has been reported in a dog[50] and some cats[24,37] with bone marrow involvement. Fungemia can be seen in acute disseminated disease[60] and is often associated with the most severe cases of systemic fungal disease.[31]

Similarly, chemistry panel results vary with the different clinical manifestations of histoplasmosis. Alkaline phosphatase,[32,50,52,60,62] alanine aminotransferase (ALT),[52] and bilirubin[22,32,39,52,60,62,73] levels may be elevated in dogs with liver infiltration. Animals with kidney involvement may have azotemia.[39] Hypoalbuminemia may occur from effects on liver function or from protein-losing enteropathy.[23,24,28,31,32,34,38,50–53,59,60,65,67,77] Hyperglobulinemia, a sign of chronic antigenic stimulation, has been reported in dogs and cats.[23,27,35,38,50,56,59,65,67,75,77] Hypercalcemia that resolves with itraconazole therapy has been reported in cats.[27] Mechanisms of hypercalcemia could include osteolytic lesions, but hypercalcemia is more likely associated with the production of calcitriol by macrophages in granulomatous inflammation.[89] Results of urinalysis are often normal.[33,34,52,60,72,75,77] However, proteinuria has been noted in dogs with renal involvement,[50,62] and very high numbers of white blood cells were noted in a dog with proliferative glomerulonephritis.[62]

Distinctive clinicopathologic abnormalities are sometimes not noted in some cases of histoplasmosis.[18] The CBC may be normal,[27,28,75] and results of chemistry panels may also be within normal reference intervals.[37,38,72,75,83]

Ancillary Tests

Skin testing for histoplasmosis involves injecting histoplasmin intradermally and monitoring the subsequent inflammatory response.[30] Skin testing has been used in surveys of animal histoplasmosis to identify animals that have been exposed and to outline geographic areas where the disease is endemic.[90] Many older references indicate that animals with disseminated disease have negative results on histoplasmin skin tests.[45,64] Although historically important, skin testing is impractical and not widely used in modern clinical settings.

Serologic tests based on complement fixation using culture filtrates of yeast and mycelial phases as antigens are available. Cross-reactivity between *Histoplasma* and *Blastomyces* spp is possible. False positives may also occur in animals with anticomplementary activity. Titers of 1:8 are considered positive.[90] Immunodiffusion testing has less cross-reactivity than does complement fixation testing and may be preferred for serologic testing.[90] Unfortunately, complement fixation and immunodiffusion serologic tests are not very effective in identifying infected dogs or cats.[37,41,45,91] In one archival study, only about 50% of dogs positive for either test had cultures positive for *Histoplasma* on necropsy.[91] Additionally, about 24% of dogs that tested negative with these tests had positive cultures.[91] Histoplasmosis should not be ruled out based on negative serology.[22]

Antigen testing (Histoplasma Quantitative Antigen ELISA, MiraVista Diagnostics, Indianapolis, Indiana) can be performed on urine, serum, airway lavage fluid, and CSF samples. This assay tests for the presence of a glycoprotein antigen released from viable *Histoplasma* yeast in body fluids adjacent to sites of infection. The protein is eliminated in the urine and may be present in urine samples.[92] Cross-reactivity with antigens from paracoccidioidomycosis, blastomycosis, and other fungal infections may result in false positives.[92] Investigation of antigen testing for blastomycosis using a similar test in dogs revealed high sensitivity and specificity[93]; however, such information has not been published for the Histoplasma Quantitative Antigen ELISA.

In humans, semi-nested polymerase chain reaction (PCR) assays are highly sensitive and specific and can detect genomic material corresponding to fewer than 10 yeast cells without cross-reaction with other bacterial or fungal pathogens.[94] PCR has been used to identify and compare *Histoplasma* in soil samples and in human and canine infections in Brazil.[6]

Culture

Diagnostic culture of *H. capsulatum* carries substantial zoonotic risk for those who handle the cultures.[95] Consequently, it should only be performed by experienced personnel in laboratories equipped to handle this pathogen. *H. capsulatum* is a slow-growing organism. Cultures are rarely positively identified before 10 days[45] and often require 10 to 20 days. Once sufficient growth is noted, identification of macroconidia and microconidia is required.[79] Blood,[60] bone marrow,[60] liver,[34,60] lymph node,[77] lung,[34,60,77] kidney,[60] pleural effusion,[53] bone,[61] joint tissue,[77] cutaneous nodule,[27,28,66] and CSF samples[66] have reportedly yielded positive culture results.

Treatment

Azoles

Azole antifungal drugs are classified into imidazoles (ketoconazole) or triazoles (fluconazole, itraconazole) depending on whether their structure contains two or three nitrogen atoms in the azole ring. The azole drugs act by inhibiting ergosterol synthesis, which is important in the construction of functional fungal cell membranes. The interaction of azole drugs with mammalian cytochrome P450 enzymes may result in hepatotoxicity and alter the metabolism of other drugs. The imidazoles are more potent inhibitors of cytochrome P450 than the triazoles. Ketoconazole and itraconazole are weak bases that require an acid environment to maximize oral absorption.[80] They should be given with food and not with antacids, except for the oral itraconazole solution, which should be given on an empty stomach.[30] Fluconazole is unique in that it has a small molecular size and low lipophilicity, which allow it to penetrate the blood–brain, blood–prostate, and blood–eye barriers.[80] Its oral bioavailability is not affected by gastric pH or the presence of food.

Although all azole drugs can be successful in the treatment of systemic fungal infections, itraconazole is the treatment of choice for histoplasmosis in cats and dogs.[30,96] The recommended dose of itraconazole is 10 mg/kg PO q12–24h. Treatment should be given for at least 4 to 6 months.[30] The oral solution may be preferred to capsules for better absorption. Pharmacokinetic studies show that 10 mg/kg/d should generate therapeutic concentrations in most cats. A 24-hour dosing interval should be sufficient; however, in some cats, 12-hour dosing may be necessary.[97]

Numerous reports document successful treatment of histoplasmosis in cats with itraconazole at 5 mg/kg q12h PO for 5 months,[38] 3 months,[28] and 6 months[28] or 10 mg/kg q12h PO for 6 months.[78] In one study,[27] treatment of eight cats with itraconazole at a dose of 5 mg/kg q12h for at least 60 days was successful. However, two of the cats required reinitiation of therapy 6 months and 10 months after discontinuation of treatment. These cats responded well to therapy again. Despite the low intraocular concentrations of itraconazole, ocular lesions resolved in all three cats treated for 3 to 6 months. Most cats in this study were previously treated with ketoconazole and were either refractory to or could not tolerate ketoconazole therapy. Thus, itraconazole seems to be more effective than ketoconazole. It was well tolerated and caused fewer adverse effects than ketoconazole in this study. The only frequent adverse effect noted was an asymptomatic mild-to-moderate increase in ALT activity.[27] Other possible side effects of itraconazole include vomiting, anorexia, and local ulcerative dermatitis due to cutaneous vasculitis.[80]

Key Facts

- Although GI signs often predominate in dogs, cats generally have signs of respiratory or disseminated disease or nonspecific signs.
- The recommended dose of itraconazole for treatment of histoplasmosis is 10 mg/kg PO q12–24h for at least 4 to 6 months.
- Possible side effects of itraconazole include an increase in ALT, vomiting, anorexia, and cutaneous vasculitis.

Although itraconazole is often the drug of choice, it is expensive, which may limit owner compliance or acceptance of long treatment regimens. Use of ketoconazole to treat cats and dogs has been reported.[3,23,24,37,75] Treatment with ketoconazole may result in adverse effects such as anorexia, lethargy, icterus, and pancytopenia.[72] Ketoconazole is also generally considered less effective than itraconazole for the treatment of systemic fungal infections (including histoplasmosis).[80]

Fluconazole penetrates into the CNS and eyes better than other azole antifungal drugs and is sometimes selected to treat cases with heavy ocular or CNS involvement.[30] However, fluconazole is not as effective as itraconazole in treating people with histoplasmosis, and it may antagonize the effects of amphotericin B.[98,99] Fluconazole is less effective than amphotericin B when used alone to treat CNS histoplasmosis in mice.[98]

Amphotericin B

Amphotericin B is a polyene macrolide antibiotic that binds to ergosterol in the cell membrane and alters membrane permeability, allowing cell contents to leak out.[80] It is an accepted therapy for histoplasmosis in dogs and cats[30]; however, it has poor bioavailability and is nephrotoxic,[80] which limits its use in veterinary medicine. Less toxic formulations of amphotericin B, including liposome-encapsulated and lipid-complexed versions, are available at a substantially higher cost. Although significantly less nephrotoxic than unaltered amphotericin B, these formulations still warrant close monitoring.[80] They can be used to achieve higher doses with less chance of developing nephrotoxicity.[96,100] The recommended dose for lipid-complexed amphotericin B (Abelcet, Enzon Pharmaceuticals; Bridgewater, NJ) is 2 to 3 mg/kg administered three times a week until a cumulative dose of 24 to 27 mg/kg is reached.[80] Lipid-complexed amphotericin B is diluted in 5% dextrose and administered intravenously.[30] Side effects during the infusion may include tremors, fever, phlebitis, and vomiting.[30] Baseline renal parameters and electrolytes should be evaluated before each dose.[80] Treatment with amphotericin B may be considered alone or in conjunction with other treatments in severe cases or in cases unresponsive to itraconazole.[30,80]

Other Therapies

Newer antifungal drugs have been investigated in humans and murine models of histoplasmosis, but not in dogs or cats. Posaconazole is a triazole that has been used successfully to treat histoplasmosis in humans.[101] Voriconazole is a triazole that has been used in humans. It is structurally related to fluconazole but has better potency and a wider spectrum of activity.[80,102] Caspofungin is an echinocandin antifungal agent that had limited effect against *H. capsulatum* (despite good activity against *Candida* and *Aspergillus* spp) in one murine study.[103]

Corticosteroid therapy has been recommended as an adjunctive therapy to reduce enlarged tracheobronchial lymph nodes in dogs with chronic pulmonary histoplasmosis.[57] Corticosteroid therapy is controversial due to the risk of immunosuppression and dissemination of active disease.[23,30–32] Animals considered for steroid therapy should have negative cytology results (i.e., no organisms detected) from transtracheal washes and bronchoalveolar lavage and should not have signs of acute histoplasmosis, including pulmonary infiltrates on radiographs or signs of systemic illness. In one report, dogs treated with prednisone (2 mg/kg PO q12–24h) with or without antifungal therapy had significantly faster improvement in clinical signs and airway obstruction, documented via bronchoscopy, than dogs that did not receive steroids. None of the corticosteroid-treated dogs developed disseminated disease or worsening clinical signs.[57]

Prognosis

Statistics on mortality from histoplasmosis have not been reported for dogs since the advent of itraconazole therapy.[71] Before the use of itraconazole in cats, the mortality rate of cats treated with ketoconazole was reported to be more than 66%.[18] In a study of eight cats treated with itraconazole, all eight cats were cured, although two cats had recurrence and responded again when therapy was restarted.[27] In general, the prognosis varies with the severity of disease and the timeliness of diagnosis and treatment. Animals with advanced disseminated disease have a guarded to poor prognosis.[96] Most authors indicate a better prognosis for pulmonary histoplasmosis compared with GI or widely disseminated disease.[48,61] With regard to the ophthalmic manifestations of histoplasmosis, blindness may occur and persist despite antifungal therapy if severe retinal changes are present.[41]

Public Health

Numerous case reports document a shared source of exposure to *H. capsulatum* for animals and humans. In one case, a man and his dog both developed pulmonary histoplasmosis after heavy exposure while cutting a dead tree for firewood.[42] In another case, a house located on the grounds of a former poultry farm became notorious for *Histoplasma* infection. The owner and four dogs developed clinical histoplasmosis, while other human family members developed positive titers for histoplasmosis. The source of the infection was not confirmed.[52] These cases demonstrate that infected pets may be a sentinel for human exposure. However, transmission of *H. capsulatum* from pets to humans has not been reported.[96] As noted above, histoplasmosis may be acquired by laboratory workers handling culture samples containing mycelial forms of the organism.[95]

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1. What variety of *Histoplasma capsulatum* is found in North America?
- **a.** *capsulatum*
- **b.** *farciminosum*
- **c.** *duboisii*
- **d.** voriconazole

2. What age group of dogs and cats is most commonly affected by histoplasmosis?
- **a.** ≤6 months of age
- **b.** ≤3 years of age
- **c.** 3 to 7 years of age
- **d.** >7 years of age

3. What is/are the most common clinical sign(s) of histoplasmosis reported in dogs?
- **a.** respiratory signs (coughing, dyspnea, harsh lung sounds)
- **b.** GI signs (diarrhea, weight loss)
- **c.** musculoskeletal signs (lameness, swollen joints, pain on palpation of bones)
- **d.** lymphadenopathy

4. What are the most common clinical signs of histoplasmosis in cats?
- **a.** nonspecific clinical signs (weakness, lethargy, emaciation, dehydration, fever)
- **b.** neurologic signs (paraparesis, seizures)
- **c.** ocular signs (chorioretinitis, anterior uveitis, retinal detachment)
- **d.** skeletal signs (lameness or swelling of one or more limbs)

5. What is the most common abnormality noted on CBCs of dogs and cats with histoplasmosis?
- **a.** neutrophilia
- **b.** thrombocytopenia
- **c.** nonregenerative anemia
- **d.** eosinophilia

6. What is the most common radiographic abnormality noted in cats with pulmonary histoplasmosis?
- **a.** interstitial pattern
- **b.** alveolar pattern
- **c.** tracheobronchial lymphadenopathy
- **d.** calcified nodules

7. Which bones appear most affected in dogs and cats with osteomyelitis of histoplasmosis?
- **a.** skull and vertebrae
- **b.** long bones of the forelimbs
- **c.** long bones of the hindlimbs
- **d.** carpus, tarsus, and immediately adjacent bones

8. What is the best way of definitively diagnosing histoplasmosis in dogs and cats?
- **a.** serology (complement fixation or immunodiffusion)
- **b.** skin testing
- **c.** identifying organism on cytology or histopathology
- **d.** antigen testing

9. What type of inflammation does histopathologic evaluation of organs affected by histoplasmosis reveal?
- **a.** neutrophilic inflammation
- **b.** granulomatous to pyogranulomatous inflammation
- **c.** eosinophilic inflammation
- **d.** lymphoplasmacytic inflammation

10. What is the treatment of choice for histoplasmosis?
- **a.** itraconazole
- **b.** ketoconazole
- **c.** fluconazole
- **d.** amphotericin B