Blastomycosis

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Abstract: For more than 100 years, blastomycosis has been recognized as causing significant morbidity and mortality in people and dogs. The disease is rare in cats. Isolation of the organism is difficult, and novel methods to culture environmental samples are forthcoming. The most significant clinical dilemma is the inability to make a timely diagnosis when multiple cytologic samples are unrewarding. This article reviews the literature on advances in epidemiology and serology, clinical presentations, new antifungal drugs, and progress in formulating a vaccine.

Blastomyces dermatitidis is a well-known, infectious, fungal organism. Blastomycosis has been characterized for more than 100 years and affects almost all mammalian species, most commonly dogs and humans. Although reported worldwide, the organism is endemic in North America. Research interests in the veterinary and human medical fields include environmental detection, serologic diagnosis, new treatments, and vaccine formulation.

Epidemiology
Veterinarians located in the Mississippi, Missouri, and Ohio river valleys as well as those located in southeastern Canada should have a high index of suspicion for this infection. The disease is endemic in most of the mid-Atlantic and southern states; states with the highest incidences include Kentucky, Louisiana, Mississippi, South Carolina, Virginia, and Washington. Northern Illinois and southern Wisconsin also have high incidence rates. In such hyperendemic areas, >1% of the total population of dogs is affected. Sporadic cases have also been reported in Colorado and New York State, suggesting a wider range of endemic areas than previously thought.

There are very few reports of the organism being isolated from nature, all using animal inoculation techniques, with thousands of cultures unsuccessfully attempted. Investigating sources of outbreaks is thus difficult. A soil isolation method using polymerase chain reaction–based detection of B. dermatitidis DNA was developed in 2006. This test yielded positive results in three out of eight soil samples near a dog kennel in Lexington, Kentucky, where 35 of 100 dogs had reportedly contracted the disease the year before. This is the first reported detection of B. dermatitidis DNA from a natural source, possibly providing a means of rapid isolation for epidemiologists at sites of outbreaks as well as possibly replacing animal inoculation techniques.

Areas from which the organism has been successfully isolated generally have acidic or sandy soil, decaying wood, and animal feces. Humidity, fog, rain, and heavy dew are thought to facilitate fungal sporulation and loosening of conidia from conidiophores. Proximity to waterways has also been implicated as a risk factor for infection.

Signalment plays a role in the occurrence of the disease in dogs, with risk factors including young age, breed (Doberman pinschers, golden retrievers, and Labrador retrievers), and possibly male sex. In humans, diagnosis of blastomycosis is four to 15 times more common in males than in females.

Pathogenesis and Clinical Presentation
The organism is primarily transmitted by inhalation of conidia that are in the mycelial phase. Infection occurs when these conidia are deposited into the alveoli, phagocytized by pulmonary macrophages, and transported to the pulmonary interstitium, where normal body temperatures promote transformation to the yeast phase. The disease may stay localized in the lungs or may spread hematogenously or lymphatically to other body systems. Dermal or lingual inoculation of the organism has also been reported, causing a localized granulomatous disease; however, this form of transmission is uncommon. The infection is not transmissible between humans, between animals, or from animals to humans and, therefore, is not considered contagious or zoonotic.

A typical case presentation is a young, male, large-breed dog presenting with coughing, tachypnea, or dyspnea. Skin lesions that appear papular or plaque-like are commonly present, occasionally with draining cutaneous tracts (FIGURE 1). Other common...
physical examination findings are lymphadenopathy, ocular abnormalities such as uveitis, and pyrexia. The disease is usually pulmonary in origin and self-limiting. However, dissemination is possible, producing a systemic, pyogranulomatous infection that can affect the lymphatics, eyes, bones, skin, central nervous and urogenital systems, and many organs, including the heart. Dogs may present with respiratory signs, a heart murmur, and a history of syncope suggestive of heart failure. Heart lesions caused by blastomycosis, although rare, can range from myocarditis to endocarditis due to pyogranulomatous and fibrous masses in and around the heart.

Blastomycosis is very rare in cats. To date, three review articles account for all of the reported cases in cats. The presentation is similar to that in dogs and does not appear to be related to immunosuppression caused by retroviruses. A 2006 study of eight cases of blastomycosis in cats revealed respiratory problems as the most common chief complaint, which is consistent with previous reports. Respiratory signs were primarily dyspnea, tachypnea, and coughing. Lymphadenopathy is generally not appreciated in cats; however, fever and skin lesions are prominent physical examination findings. Skin lesions reported in cats are mostly dermal masses on the head and trunk. Ocular abnormalities such as retinal granulomas and retinal detachment are reported to occur in 18% to 32% of cases. Central nervous system disease is relatively common in cats with systemic blastomycosis and carries a poor prognosis.

**Diagnosis**

**Hematology**

Routine hematologic screens are nonspecific for the diagnosis of blastomycosis. However, high band neutrophil counts have been correlated with decreased survivability in canine patients with pulmonary blastomycosis.

**Cytology**

Cytologic identification of blastomycosis organisms is the gold standard and most common method of diagnosis. However, this method has variable sensitivity, and multiple cytologic or histologic samples may be needed for a diagnosis to be confirmed. A 2008 study indicated that transthoracic fine-needle aspiration is more sensitive (81%) than transtracheal washing (69%) for obtaining a diagnostic sample in dogs with pulmonary blastomycosis.

**Radiology**

A diffuse miliary or nodular interstitial pattern has been reported as the most common radiographic manifestation of pulmonary blastomycosis. In a 2008 study of 125 dogs with pulmonary blastomycosis, most dogs (59%) had localized infiltrates rather than diffuse, nodular, interstitial disease. These nondiffuse patterns could mimic bacterial pneumonia or neoplasia, highlighting the need for a confirmatory diagnosis. Tracheobronchial lymphadenopathy is seen in 25% to 29% of cases and is not correlated with extent of lung disease or survival times. In the study of 125 dogs, the number of affected lung lobes was the only radiographic finding that was found to be significantly correlated with decreased survivability. Of the 125 dogs in the study, 88% of dogs with fewer than four lobes affected survived compared with 52% of dogs with four or more lobes affected.
Serology

Antibody Detection
Serologic tests that detect antibodies evaluate the humoral immune response, which is not always indicative of active infection and varies among patients. The most widely available serologic tests to detect antibodies in veterinary medicine is agar gel immunodiffusion (AGID), which has a reported sensitivity ranging from 17.4% to 90%. A study testing the antibody responses of dogs with confirmed blastomycosis used a novel radioimmunoassay (RIA) and compared the results with those from the traditional AGID test. The reported difference in sensitivity was striking: 92% and 41% for the RIA and AGID methods, respectively.

Antigen Detection
Because up to 30% of dogs lack detectable antibodies at the time of presentation, studies are now looking at antigen assays as a method of detecting B. dermatitidis infection. MiraVista Diagnostics (Indianapolis, IN) has developed an EIA for detecting antigen in serum and urine specimens (MVista Blastomyces dermatitidis quantitative antigen EIA). Urine specimens from people with blastomycosis and other fungal infections were used in studying this test. The study used paired canine urine and serum specimens of 46 confirmed blastomycosis cases and 44 control cases negative for fungal infection. Urine specimens
yielded a sensitivity of 93%, whereas serum specimens yielded a sensitivity of 87%. The specificity was excellent (100%) for both specimen types using the negative controls. Cross-reactivity with other fungal organisms was not investigated in this study. The findings of this study are promising for the use of EIA antigen testing in the early diagnosis of blastomycosis in dogs.

**Treatment**

The treatment for blastomycosis depends on the severity of disease. If significant pulmonary compromise is present, amphotericin B is recommended along with itraconazole for the first 4 to 7 days, followed by itraconazole for 4 to 6 months or 1 month past radiographic resolution.\(^{14,20}\) In less severe cases, itraconazole alone is recommended for at least 60 days or 1 month past resolution of clinical or radiographic signs of disease.\(^{21}\) Ketoconazole is less effective than itraconazole; however, if cost of treatment is a concern, antibody response is not protective.\(^{29}\)

Studies are ongoing in formulating an effective and safe vaccine against blastomycosis. Early studies used a recombinant BAD1 (an immunodominant surface antigen) vaccine to initiate an immune response.\(^{24}\) The increase in survival time of vaccinated mice infected with Blastomyces dermatitidis in a dose-dependent fashion.\(^{24}\) With its wide tissue distribution, this drug may be effective in treating central nervous system blastomycosis; it has been successful in treating a human case of cerebral blastomycosis.\(^{27}\) Posaconazole is an analogue of itraconazole. This drug improved survivability in mice infected with *B. dermatitidis* compared with itraconazole, fluconazole, and amphotericin B.\(^{23}\) Also, samples of lung tissue that were obtained and cultured after treatment with posaconazole were negative for *B. dermatitidis*.\(^{23}\)

A recombinant, live attenuated vaccine has also been formulated. Mice injected subcutaneously with live yeast of this mutant strain of *B. dermatitidis* had significantly improved survival when challenged with nonmutant *B. dermatitidis*.\(^{30}\) This genetically engineered strain of *B. dermatitidis* shows promise in the future of vaccines against the organism, both therapeutically and preventively. This vaccine is being evaluated for trials in human volunteers.\(^{1}\)

**References**

Blastomycosis

1. What currently available test method is the most sensitive for diagnosing *B. dermatitidis* infection?
   a. AGID antibody test
   b. EIA antigen test
   c. cytology of lung aspirate
   d. chest radiography

2. Patients with blastomycosis may present with
   a. uveitis.
   b. neurologic signs.
   c. heart murmur.
   d. all of the above

3. Blastomycosis is transmitted primarily by
   a. dermal inoculation
   b. contact with other infected animals
   c. inhalation of fungal conidia
   d. ingestion of fungal conidia

4. Which diagnostic test is most commonly used in clinical practice to diagnose blastomycosis?
   a. serology
   b. histopathology
   c. fungal culture
   d. cytology

5. Which method is most likely to obtain a diagnostic sample for cytology?
   a. transtracheal wash
   b. transthoracic fine-needle aspiration
   c. impression smear of nasal discharge
   d. pharyngeal swab

6. What is the overall treatment success rate for blastomycosis?
   a. 25% to 35%
   b. 45% to 55%
   c. 70% to 80%
   d. 90% to 100%

7. In cats, the most common physical examination finding related to blastomycosis is
   a. lymphadenopathy.
   b. neurologic impairment.
   c. ocular abnormalities.
   d. respiratory problems.

8. Which is the drug of choice for treatment of uncomplicated blastomycosis?
   a. itraconazole
   b. amphotericin B
   c. fluconazole
   d. voriconazole

9. A negative prognostic indicator for dogs with pulmonary blastomycosis is
   a. an alveolar pattern.
   b. tracheobronchial lymphadenopathy.
   c. involvement of four or more lung lobes.
   d. an interstitial pattern.

10. The most common radiographic finding(s) in pulmonary blastomycosis is/are
    a. a diffuse interstitial pattern.
    b. a localized infiltrative pattern.
    c. tracheobronchial lymphadenopathy.
    d. a and b

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