Blastomycosis

Shaun K. Morris, B.Sc.H., M.D.
Claire K. Nguyen B.Sc.N., R.N., M.Sc.

Abstract

Blastomycosis is an infection caused by the dimorphic fungus *Blastomyces dermatitidis. B. dermatitidis* is endemic to the regions surrounding the lakes and waterways of central North America including Ontario. While Blastomycosis predominantly causes infection of the lungs, it may affect virtually any organ system. Diagnosis and initiation of treatment is often delayed, as clinical presentation may resemble a number of more commonly encountered conditions. Evidence from small case series suggests that itraconazole is the first line medication in the majority of adult infections, and intravenous amphotericin B is the medication of choice in life threatening or disseminated infections and in children.

Introduction

Blastomycosis is a relatively rare but potentially lethal fungal disease with an endemic focus in central Canada including Ontario. First described as a skin infection by Gilchrist[1] in Baltimore in 1894, blastomycosis is a chronic granulomatous disease caused by the thermally dimorphic fungus *Blastomyces dermatitidis* that is endemic to central Canada and the United States. *B. dermatitidis* causes disease in both humans and animals, most commonly canines. Unlike many fungal infections, *B. dermatitidis* is a primary pathogen that may cause disease in individuals with intact immune systems. The clinical presentation is variable and may mimic that of other diseases. The most common presentation is pulmonary infection. Acute infection may resemble a bacterial pneumonia whereas chronic involvement appears similar to lung cancer or tuberculosis. Extrapulmonary sites of infection include the skin, bone, and central nervous system (CNS). Rare sites of infection include the genitourinary system, the liver and the kidneys. While described as one of the most important endemic mycoses in North America, the ecology and epidemiology of *B. dermatitidis* is poorly characterized.[2]

Microbiology

The fungal organism exists in two forms: a sexual form named *Ajellomyces dermatitidis* and an asexual form, *B. dermatitidis*.[3] The asexual form exhibits thermal dimorphism. At room temperature, it grows as a mycelial form and at 37ºC it grows as a yeast.[4] Grossly, the yeast colony is cream or tan in colour. Microscopically, the yeast form has several distinguishing characteristics. It appears as a large, round organism up to 20 mm in diameter with up to 12 nuclei, has a thick cell wall and reproduces by a single large, wide-based bud. Identification of these characteristics in a clinical sample suggests a diagnosis of blastomycosis. The mycelial form appears white to grey-brown with a silky appearance. Microscopically, the mold shows branching hyphae 2 to 3 mm in diameter with conidiophores ending in single terminal conidia.[3] The conidiophores branch at a right angle from the main hyphal segment. Definitive diagnosis is made by conversion of the organism to yeast form at 37ºC. Unlike other disease-causing fungi, *B. dermatitidis* does not colonize humans and retrieval from tissue confirms infection.

Epidemiology

The ecology and epidemiology of the disease is poorly understood and has been hampered by difficulty in isolating *B. dermatitidis* from natural sites, and the lack of an effective skin test. As is the case with other dimorphic fungi, it is presumably a soil organism that exists in nature in the mycelial form. Environmental temperature does not seem to be as important to the organism as favourable microenvironment conditions, including moist soil with a proximity to water, a high content of organic material, an acidic pH, and exposure to animal excreta.[5,6] Study of sporadic cases and occasional outbreaks indicate that in North America, blastomycosis occurs primarily in the southeastern and south-central states bordering on the Mississippi and Ohio rivers' basins, the states and provinces bordering the Great Lakes and small regions surrounding the St. Lawrence River.[7] Worldwide, cases have been reported in England, Switzerland, Poland, the Middle East, India, and Africa.[3] However, the great majority of cases are from the eastern portion of North America.

The incidence of blastomycosis is not reliably known as it is not nationally reportable in either Canada or the United States. Blastomycosis was removed from the list of reportable diseases in Ontario in 1989.[8] However, it remains reportable in Manitoba, Wisconsin, and Northwestern Ontario.[9] A recent study[10] demonstrated that the Kenora, Ontario census

division has the highest annual incidence (7.11 cases per 100 000 population) of blastomycosis of any geographic region of similar size in North America. This is in comparison to rates of 1.4 cases per 100 000 population in Wisconsin[9] and 1.3 cases per 100 000 population in Mississippi.[11] A report from the Population and Public Health Branch of Health Canada[12] suggests a region of hyperendemicity in the Kenora, Keewatin, and Jaffray Mellick tri-municipal area (104.9 per 100 000) and the surrounding Aboriginal reserves (404.9 per 100 000). This study also showed that incidence rates increased suddenly at a significant level beginning in 1998. A review[12] of 143 cases of blastomycosis diagnosed in Manitoba from 1988 through 1999 (84 from residents of Manitoba and 59 from residents of northwestern Ontario) described a mean annual incidence of 0.62 cases per 100 000 population in Manitoba with the highest incidence being in the southern half of the province. There does not exist any published literature describing the incidence of blastomycosis in provinces other than Ontario and Manitoba. Although *B. dermatitidis* is not considered to be endemic in any urban environment, there exist case reports of children diagnosed with blastomycosis who have not traveled outside the Greater Toronto Area.[13]

Case series have consistently described males to be more commonly infected than females. Incidence rates also appear to be higher in Aboriginal populations than in non-Aboriginal populations.[10,12] These differences are felt to be due to increased risk of exposure through work, residential activities and environment of habitation rather than from any inherent differences in sex or race.

Blastomycosis can occur year round, however the Canada Population and Public Health Branch study of the Kenora catchment area describes an increased likelihood of onset between September and January.[12] Given the incubation period of the disease, this may indicate an increased likelihood of infection during the months of summer and early fall, the period of highest rainfall and least snow cover in the region. This is consistent with factors previously proposed as favourable for *B. dermatitidis* growth.[5,6]

Pathogenesis

The literature describes five methods of transmission of blastomycosis: inhalation, accidental inoculation, dog bites, sexual, and maternal-fetal.[3] Of these, by far the most common is inhalation. Conidia become airborne when the mycelial culture is disturbed. Upon inhalation, conidia settle in the lungs and initiate an inflammatory response of neutrophils and macrophages. Inhalation of conidia appears to cause infection in about 50% of individuals. Neutrophils and macrophages have been shown to kill up to 90% of conidia, however those that survive the initial inflammatory response change into the yeast form, which are more resistant to phagocytosis.[14,15] Proliferation and granuloma formation occurs over 4 to 8 weeks. Unlike tuberculosis, the granuloma of blastomycosis does not caseate.[16] Once established in the lung, the fungus may spread hematogenously to the bone, skin, or other organs. Mortality in patients with systemic infection who receive appropriate antifungal therapy is between 6% and 10%.[10,11,25,26]

The vast majority of patients with blastomycosis are immunocompetent. However, immunocompromised patients, including those with AIDS, transplants, and those being treated with systemic corticosteroids, have been reported.[4] There are also reports of an increased percentage of cases in immunocompromised patients from 1978 to 1991 compared to 1956 to 1977.[4] It is unclear if this is due to a referral bias or an increase in the number of immunocompromised individuals living in endemic regions.

At least two studies have found the incidence of infection to be highest in the 50-59 and 60-69 year old age groups.[10,11] The apparent increased risk of infection in older individuals has been proposed to be due to a decrease in function of the cellular branch of the immune system. While it is clear that immunocompetent individuals are at risk of infection with *B. dermatitidis*, further research is required to delineate the effect on infection and progression of disease in the sub-populations with varied types of immune system dysfunction.

Clinical Manifestations

Blastomycosis has been called "a great masquerader"[17] due to its very non-specific initial presentation. Early symptoms consist of fever, malaise, myalgias, weight loss, cough, and pleuritic chest pain. While virtually any body system may be infected, pulmonary involvement is most commonly seen. A recent study examining the clinical spectrum of blastomycosis diagnosed at Manitoba hospitals found that 93% of 133 patients had lung involvement.[10] Blastomycosis lung disease may take many forms. Pulmonary radiology can demonstrate lobar inflammation similar in appearance to a bacterial pneumonia, large masses suggestive of bronchogenic carcinoma, or miliary infiltration indistinguishable from tuberculosis. Because of lack of specificity in appearance, pulmonary plain film radiology is not diagnostic of this infection. Pleural involvement has been found in 25%-42% of patients though massive pleural effusions appear to be quite rare.[18,19] Onset of symptoms may be either acute or chronic. In a series of 26 patients, eight initially had an acute pneumonia and 16 presented with a chronic pulmonary infection.[18]

As with pulmonary involvement, blastomycosis cutaneous lesions may appear very similar to more commonly encountered conditions including basal cell carcinoma, squamous cell carcinoma, pyoderma gangrenosum, keratoacanthoma, or panniculitis. Cutaneous lesions may be either ulcerative or verrucous. Ulcerative lesions generally exhibit sharp, heaped up

borders and a base containing exudates. Verrucous lesions have a sharp, raised, irregular border. The verrucous form often has crusting above an abscess in the subcutaneous tissue.[16] Even in the absence of clinically apparent inflammation in the ulcer, biopsy of the subcutaneous tissue demonstrates micro abscesses and shows organisms on microscopy and culture.[4]

Osteomyelitis due to blastomycosis has been reported in up to 25% of diagnosed individuals.[20] Sites involved most commonly include the long bones, vertebrae, ribs, skull, and pelvis. Genitourinary disease may rarely occur in the prostate, testicle, ovary, and endometrium. CNS involvement may include meningitis or intracranial abscesses.

Diagnosis

There is no clinical syndrome diagnostic of blastomycosis and diagnosis may only be made following microbiological isolation or observation of the organism from a clinical specimen. Once a suitable specimen has been obtained, fluorescent stains such as FungiFluor™ that bind to chitin may be used to identify the classic morphology of *B. dermatitidis*. In an appraisal of diagnostic techniques in 55 confirmed cases of pulmonary blastomycosis[21] at the Mayo Medical Centre, a high diagnostic yield (86% per patient) was obtained by culture of specimens obtained via non-invasive methods (sputa, tracheal secretions, and gastric washings). The diagnostic yield of flexible bronchoscopy was 92%. These results suggest that in the majority of cases, diagnosis can accurately be made through non-invasive means. Bronchoscopy should be performed in patients in whom sputum is negative. Should bronchoscopy return negative but clinical suspicion remain high, more invasive procedures such as thoracoscopy or thoracotomy may be considered to obtain culture positive samples. However, the average time to culture confirmation is approximately 5 weeks.[22] Clearly, a more rapid diagnostic technique would be of benefit. The authors of the Mayo study concurred with previous work that found serological methods to be poorly sensitive and suggested that Papanicolau staining of respiratory samples, shown to have a high diagnostic yield,[22] be used in *B. dermatitidis* endemic regions as a rapid diagnostic test.

When infection is extrapulmonary, surgical tissue samples are generally required for microbiological investigation leading to diagnosis.

Treatment

Prior to the advent of antifungal medications, chronic pulmonary blastomycosis was associated with mortality rates of up to 60%.[3] All cases of chronic infection should thus be treated aggressively with antifungal medication. Evidence suggests, however, that acute pulmonary infection may be self-limiting in immunocompetent individuals.[23] In individuals who appear to have undergone spontaneous resolution, careful follow up may be adequate management. However, recent treatment guidelines[24] proposed by consensus opinion of an expert panel state that all patients who are immunocompromised, have progressive pulmonary disease, or extrapulmonary disease should be treated. Initial choice of medication in mild to moderate pulmonary or extrapulmonary (excluding CNS) infection is recommended to be itraconazole. When used for blastomycosis, itraconazole has enhanced antimycotic activity, improved pharmacokinetics, and has a better side effect profile than other azole medications.[24] Intravenous amphotericin B is the first line medication in life-threatening pulmonary or CNS infection in immunocompromised individuals, and those who do not tolerate or fail azole therapy. Amphotericin B is also the drug of choice in pregnant women due to the potential for teratogenicity with azoles. Therapy should continue for a minimum of 6 months in mild to moderate infections and a minimum of one year in severe infections or infections of bone.

Blastomycosis in Children

Blastomycosis appears to be uncommon in children and it has been reported that less than 2% of cases occur during childhood.[25] However, the Kenora report found 36% of Aboriginal patients admitted to hospital and diagnosed with the disease to be under the age of 13 years.[12] Clinical and therapeutic information specific to this group is minimal. A review of the literature found four small case series of blastomycosis in the pediatric population in the United States.[25,26,27,28] There have been no case series of the disease in the pediatric population from Canada. It has been suggested that children may be less likely to respond to initial therapy with an azole than adults and that amphotericin B should be the first line choice.[26] One study reported a greater incidence of disseminated infection in children than in adults[25] while another reported no cases of disseminated disease in a series of 14 children.[28] Further investigation of blastomycosis in children is required to determine the range of clinical presentations and effectiveness of various treatments, as well as the incidence of disease in this patient group.

Summary

Blastomycosis is a potentially lethal fungal disease endemic to central North America including Ontario. In southern Ontario, the majority of infections occur in individuals who live in or visit the region surrounding Georgian Bay. In western Ontario, in the region surrounding Kenora, blastomycosis occurs at a rate far exceeding that documented anywhere else in the world. While the ecology of the infecting organism, *B. dermatitidis*, is poorly understood, those most at risk appear to be individuals spending time outdoors in wooded areas in close proximity to water.

Blastomycosis presents a diagnostic challenge as it may closely resemble much more commonly encountered clinical con-

ditions. Above all else, a high degree of clinical suspicion is required to make a timely diagnosis. Blastomycosis should be included in the differential diagnosis of any individual who resides in or has traveled to an endemic region. For this reason, it is important that clinicians have a basic awareness of the epidemiology of the fungus. Blastomycosis should be considered as a diagnostic possibility in individuals who are being treated appropriately for presumed bacterial infections but are not showing signs of clinical improvement, those with presumed pulmonary malignancies and individuals with characteristic skin lesions who have spent time in endemic regions. Current treatment regimens, outlined in this paper, have dramatically improved the outcome of blastomycosis infection. However, there remains a great deal to be learned about *B. dermatitidis* and its epidemiology. The apparent increase in incidence of blastomycosis, shown by recent Canadian studies,[10,12] suggests that it may be appropriate to once again list the disease as reportable in this country. This would facilitate gathering of data and contribute to more effectively understanding the ecological niches of *B. dermatitidis* and informing clinicians of higher risk geographic regions and populations.

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