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PULMONARY BLASTOMYCOSIS: AN OVERVIEW

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ABSTRACT
Blastomycosis is an uncommon disease, with most reported in North America. The endemic areas are the Mississippi and Ohio river valleys. Pulmonary blastomycosis is more common than extrapulmonary blastomycosis. Although largely unknown, inhalation of spores from the soil is considered to be the route of infection. Most cases of pulmonary blastomycosis are asymptomatic, when symptomatic minimal respiratory symptoms are the most common presentation. Severe disease, including dissemination and acute respiratory distress syndrome, can occur in immunosuppressed patients. Urinary antigen testing and antibody assays are of poor diagnostic specificity; culture and identification of the organism are necessary to confirm the diagnosis. Amphotericin B and itraconazole are the mainstays of treatment, and treatment recommendations vary based on the patient's immune status and severity of the infection.

KEYWORD: Blastomycosis, pulmonary, fungus.

INTRODUCTION
Blastomycosis is an uncommon disease, with most reported cases from the United States (USA) and Canada. Rarely cases have been reported from African countries and India.[1,2] One to two cases per 100,000 is the average incidence of blastomycosis in states where it is reported in the USA.[3,4] States endemic for the disease include Arkansas, Kentucky, Mississippi, and Wisconsin; among them, Wisconsin reports the greatest number of cases.[5] Wisconsin is also the state with the highest number of blastomycosis outbreaks reported in the last century; at least nine of the fifteen reported since 1953. The endemic areas can be traced to the Mississippi and Ohio river areas and the Great lakes.[6,8] Except in Wisconsin, Arkansas, Louisiana, Michigan, and Minnesota, blastomycosis reporting is not mandatory, making the exact epidemiology of the condition largely unknown. Underdiagnosis of asymptomatic and mild cases is yet another factor underestimating the incidence of blastomycosis. Although B.dermatitidis has not been isolated from the soil as commonly as Histoplasma capsulatum, there were instances of isolating B.dermatitidis from the soil in association with epidemics.[8,9] The presence of moist soil was common for all instances of isolation of B.dermatitidis. A recent report of two cases of pulmonary blastomycosis from Colorado after significantly above-average rainfall in the region reinforces the association of wet soil and the presence of B.dermatitidis in the soil.[10] Cell-mediated immunity is the most crucial aspect of the body's defense against any fungal infection, which is valid for blastomycosis also. There are reports of severe and fatal blastomycosis infections in human immunodeficiency virus (HIV) infected patients but it is still rare compared to other dimorphic fungal infections.[11] Increased risk of infection among the black population has been described in some studies and the authors suggested genetic risk factors predisposing to this ethnic predisposition, but it has not been proven yet.[12,13] The age group most commonly affected is 30 to 50; pulmonary blastomycosis is extremely rare in children.[14] Human to human or animal to human transmission of blastomycosis has not been reported.

Pathology
Blastomyces is a dimorphic fungus with yeast and mold forms. The conidia of the Blastomyces mold are the infectious phase, and inhalation of these conidia after disruption of soil is the first step toward potential infection.[15] The pulmonary infection results from inhalation of the conidia into the lungs, where natural resistance is mediated by neutrophils, monocytes, and alveolar macrophages that can phagocytize and kill the conidia.[16] Conidia that escape this natural defense are rapidly converted into yeast forms in the tissues, which are more resistant to phagocytosis and killing.[17] The yeast form's thick cell wall has been suggested to be antiphagocytic and may contribute to its virulence. Specific chemical and structural components of the cell

wall have also been associated with virulence, including the lipid and phospholipid content.[18,19]

Other important factors contribute to the virulence of the yeast form of B dermatitidis. A novel 120-kd glycoprotein antigen (WI-1) localized on the cell wall surface is identified. WI-1 is the major immunodominant epitope for humoral and cellular immunity.[20,21] WI-1 also functions as an adhesin that can bind to CR3 and CD14 of human macrophages.[22] This adhesion activity is mediated by a 24–amino acid tandem repeat that is 90% homologous with the Yersinia adhesin called invasion.[23] The carboxy-terminal end of WI-1 contains a cysteine-rich domain similar to epidermal growth factor and may also mediate binding to extracellular matrix.[23] WI-1 quantity and shedding in a wild-type (virulent) strain and two mutant B dermatitidis isolates, which are hypovirulent in a murine model of infection, are compared.[24]

Mutant strains expressed more WI-1 on their cell surface, shed less into the medium, and had twofold to threefold greater binding of the yeast form to macrophages, the latter of which was blocked by anti–WI-1 monoclonal antibody. In further studies using the same three strains, it is proven that the quantity of 1,3-a-glucan was reduced, and its distribution was different in the hypovirulent strains.[25] In more recent studies, the WI-1 gene is genetically disrupted, which resulted in impaired binding and entry of the organism into macrophages and loss of adherence to lung tissue.[26] The WI-1 mutant was also avirulent in a murine model. When WI-1 was restored to the mutant organism, all functions were restored.[26] These studies collectively indicate that WI-1 is an important virulence factor for B dermatitidis. However, other cell wall components such as 1,3-a-glucan may modulate virulence by their effect on WI-1–mediated interactions between the yeast cell and host cell. Humoral immunity against B dermatitidis does not confer resistance to or hasten recovery from disease.

In contrast, the major acquired host defense against B dermatitidis is cellular immunity, mediated by antigen-specific T lymphocytes and lymphokine-activated macrophages. Cellular immunity can be induced in mice by the subcutaneous injections of live or heat-killed B dermatitidis.[27] Further, resistance to infection has been shown to parallel cellular immunity development, and resistance to infection in mice has been transferred by T lymphocytes [28-29] The development of cellular immunity has also been documented clinically by antigen-induced lymphocyte proliferation against various Blastomyces antigens.[21,30,31] More recent studies have used a genetically engineered strain of B dermatitidis, which lacked WI-1 and was not pathogenic, as a live attenuated vaccine in a murine model.[32] Administration of the vaccine strain not only induced delayed hypersensitivity but also protected animals against lethal pulmonary infection.[32]

Histopathological specimens, mostly from animal studies, demonstrated suppuration similar to bacterial pneumonia with some granulation tissue.[33] The granuloma formed is noncaseating and is challenging to differentiate from sarcoidosis in the pathological specimen.[34]

Clinical features

The clinical presentation of pulmonary blastomycosis can be varying depending on the immunity of the patient. The clinical features can be grossly divided into acute pulmonary blastomycosis and chronic pulmonary blastomycosis. In most cases, acute pulmonary blastomycosis presents with features of acute respiratory infection; Fever, cough, myalgia, arthralgia, and pleurisy are the most common presenting complaints.[35] Cough is often productive with or without hemoptysis. In rare occasions, the incidental radiographic abnormality may be the only initial clue to pulmonary blastomycosis.[36] There are reports of asymptomatic cases diagnosed after screening exposed population during epidemics of blastomycosis.[37] The initial acute presentation may be indistinguishable from acute bacterial community-acquired pneumonia, and many patients end up receiving antibacterial medications before the diagnosis of blastomycosis is considered.[38]

Chronic pulmonary blastomycosis can be the initial presentation or can follow an acute illness. Chronic pulmonary blastomycosis presents with a 2- to 6-month illness with weight loss, fever, night sweats, cough with sputum, and chest pain. Mass-like pulmonary infiltrates may be more common in patients presenting with chronic illness.[39] This illness may be misdiagnosed as pulmonary tuberculosis, chronic pulmonary histoplasmosis, or malignancy. The organism can remain in the lungs for years to reactivate at a later stage. Miliary blastomycosis or endobronchial spread of infection is another unusual presentation of chronic pulmonary blastomycosis, often leading to acute respiratory distress syndrome (ARDS) with a very high mortality rate.[40]

Extrapulmonary features of disseminated blastomycosis, including skin, bone, genitourinary, and central nervous system involvement, can help prevent blastomycosis as a diagnosis. Although blastomycosis is unusual in patients with immunodeficiency, when blastomycosis occurs in immunocompromised patients, the disease is more aggressive than in immunocompetent hosts.[41] Among patients with acquired immune deficiency syndrome (AIDS) ,blastomycosis tends to be a severe illness with widespread dissemination, often including the CNS and is associated with a high rate of early mortality.

Diagnosis

The majority of patients with blastomycosis, whether symptomatic or not, have alveolar or mass-like infiltrates on chest radiography.[42] The infiltrate's specific location is not particularly helpful diagnostically, although the

upper lobes may be involved most often.[39] Mass lesions mimic malignancy, so physicians in endemic areas must include blastomycosis in the initial differential diagnosis for a patient with presumed lung cancer. Reticulonodular and miliary radiographic patterns and solitary nodules are seen less often than alveolar and mass-like infiltrates. Cavitation of the lung parenchyma is uncommon relative to that seen with tuberculosis, histoplasmosis, and coccidioidomycosis.[36] The definitive diagnosis of blastomycosis is only possible with culture of the organism. Sputum, bronchial washings, bronchoalveolar lavage, deep tissue biopsy specimen, scrapings, exudate, joint fluid, synovial tissue biopsy specimen, bone biopsy, prostate biopsy specimen, urine, cerebrospinal fluid can be used as specimens for culture. Techniques that enhance fungal elements' visibility include the use of a potassium hydroxide (KOH) solution that shows the round shape, doubly refractile wall, and single broad-based bud. Periodic acid schiff (PAS) stained section of the lesion shows a budding yeast of B. dermatitidis with the characteristic broad-based bud and a single nonbudding yeast cell.[36] Enzyme immunoassays, the most recently developed antibody detection tests, are more sensitive than immunodiffusion for diagnosis of blastomycosis but less specific.[43]

Treatment

The treatment recommendations for blastomycosis in the united states are published by the infectious disease Society of America (IDSA), with the last update in 2008.[44] The recommendation is based on the site and the severity of the infection, and the patient's immune status. IDSA also recommends a particular regimen for pregnant women and children. Although the disease can be self-limited in immunocompetent patients, IDSA recommends considering treatment to prevent the chance of extrapulmonary dissemination.

In an immunocompetent and non-pregnant adult, for treating moderate to severe pulmonary blastomycosis, IDSA recommends initial treatment with amphotericin B for one to two weeks or until improvement, followed by oral itraconazole for six to twelve months. For mild to moderate disease, IDSA recommends oral itraconazole for six to twelve months.

In immunosuppressed patients, regardless of the severity, IDSA recommends amphotericin B for one to two weeks or until improvement is noted, followed by itraconazole for at least 12 months. IDSA also recommends considering lifelong therapy with itraconazole if immunosuppression is not reversible. For pregnant women, a lipid formulation of amphotericin B is the treatment of choice. Azoles should be avoided to prevent possible teratogenicity.

In all the patients, IDSA also recommends checking serum levels of itraconazole one to two weeks after therapy initiation to confirm adequate drug exposure. A baseline complete blood count, hepatic and renal function panel is advised to monitor medication's adverse effects. However, no major societies provide guidelines on timing and frequency for monitoring. Azoles are cytochrome P450 inhibitors and have the potential for many other drug-drug interactions; the clinician should carefully review the patient's medication list before initiating treatment with azoles.[45]

CONCLUSION

Precise data on the prognosis of pulmonary blastomycosis is unavailable due to the disease's rarity and varying disease manifestations. Disseminated blastomycosis, blastomycosis in immunocompromised patients, and blastomycosis induced ARDS has a higher reported mortality.[46-47] Reported case fatality range from 4% to 22% depending on the population.[48] Recurrence of the disease is rare after appropriate treatment.

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