Blastomycosis Arthritis

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Introduction

Blastomycosis is a rare systemic fungal infection caused by the thermally dimorphic fungus *Blastomyces dermatitidis*, which is endemic in forested areas of the United States and Canada. This fungus is generally found around large lakes and along the Mississippi and Ohio river valleys, although cases have also been described in other parts of the world [1–3]. Usually, the disease affects the lungs, skin and other soft tissues; however, within fungal diseases, blastomycosis shows a special predilection for bone. This microorganism can cause arthritis directly by hematogenous spread or through contact with an affected bone [4]. When a diagnosis is made in a timely manner, bony and articular blastomycosis responds favorably to antifungal drugs with or without surgical debridement. The key to timely diagnosis is to maintain a high index of suspicion and a low clinical threshold to obtain appropriate microbiological samples [1].

Case Definition

Patients with blastomycosis frequently show joint symptoms; however, arthritis is rarely documented through synovial fluid analysis. Reports of joint involvement are unusual, and joint involvement has only rarely been described as the initial presentation of a disseminated disease [5]. Cases of mono-, oligo- or polyarthritis due to blastomycosis have been reported as the form in which the disease first presents [5–7]. Arthritis is defined as pain, limitation in the range of motion and synovial effusion in a joint. Additionally, the diagnosis of joint infection by blastomycosis usually requires a positive culture from synovial fluid or microscopic evidence of yeast in the synovial fluid, plus another positive culture from elsewhere in the body [5].

Epidemiology

The vast majority of confirmed cases of blastomycosis come from the United States and Canada, although cases have also been reported in Africa, Asia, Europe and Latin America [8–13]. The disease is endemic in the southern regions and in the northern part of the central United States. The main affected areas in North America are the Mississippi and Ohio River valleys as well as Manitoba, Ontario and around the Great Lakes. In general, blastomycosis is a rare disease. However, it does not require mandatory national reporting in all states. In states that do have mandatory reporting, the annual incidence rates range from approximately one to two cases per 100,000 inhabitants. Wisconsin has the highest incidence rate, ranging from 10 to 40 cases per 100,000 people per year in several northern counties [14, 15]. It is estimated that three to six cases requiring hospitalization per one million inhabitants occur annually in endemic areas [16].

Bone and joint symptoms are common in patients with blastomycosis, although true arthritis is much less frequent. In several large case series, bone involvement has been present in approximately 25–60% of patients with disseminated blastomycosis. The actual incidence of joint blastomycosis is unknown, although it is estimated to range from 3% to 8% [5, 13, 17].

Etiological Pathogenesis

The microorganism normally exists in the mold phase in the environment. Conidia of the fungus are aerosolized during activities that involve the movement of soil or decaying vegetation. Infection is acquired mainly after inhalation of the fungus, although infection by direct inoculation after trauma

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may also occur [18]. In the lungs, inhaled conidia that evade the innate immune response, such as through phagocytosis mediated by macrophages and neutrophils, move to the yeast phase causing a respiratory infection [1, 18].

The initial innate immune response and subsequent cell-mediated immune response produce a granulomatous tissue response that can be seen in the lungs, skin and other organs. After conversion to the yeast phase, the microorganism can be disseminated hematogenously [18].

With respect to joint involvement that can occur in this disease, two possible mechanisms of fungal invasion have been proposed. Direct invasion leading to osteomyelitis from the spread of a contiguous focus of infection is clearly recognized, but it is also postulated that the fungus can enter joints through hematogenous spread [4, 19].

Clinical Manifestations

The most frequent clinical manifestation of infection by *B. dermatitidis* is lung infection, which occurs asymptomatically in approximately 50% of cases. In most cases, the disease manifests as a mild, self-limiting lung infection that occurs 2–3 weeks after exposure to the pathogen. Patients who are ill enough to seek medical attention are treated with antibiotics for an alleged community-acquired pneumonia. The most common presenting symptoms of pulmonary blastomycosis are cough, fever, night sweats, weight loss, chest pain, dyspnea, myalgias and hemoptysis. Chest x-ray may show areas of pneumonitis, mass-type infiltrates or nodules; hilar or mediastinal lymphadenopathies are observed rarely. Although the infection can be self-limiting, it is now recommended to treat all symptomatic persons in whom the diagnosis has been made to prevent progression to disseminated disease [20].

Chronic presentation forms are indistinguishable from tuberculosis or lung carcinoma [21]. Rarely, patients with pulmonary blastomycosis can develop acute respiratory distress syndrome (ARDS), which has been reported in both immunocompromised patients and previously healthy people. The diagnosis of blastomycosis is often delayed in many of these cases and is associated with a high mortality despite receiving the appropriate treatment [20].

The microorganism *B. dermatitidis* can spread to many different organs; the skin, bone and genitourinary systems are the most frequently affected. Early dissemination occurs in a large proportion of patients, although most remain asymptomatic. When extra-pulmonary manifestations appear, chest x-ray may remain normal or show only a residual process. Skin lesions often appear on exposed areas of the head, neck and extremities. The typical lesion appears as a crusted verrucous plaque with central microabscesses, although nodules, ulcers and pustules have also been described. There are usually multiple cutaneous lesions [22].

Involvement of the genitourinary tract occurs more frequently in men, with the prostate being the most commonly affected organ. Typical symptoms include dysuria and an obstructive syndrome. The central nervous system may also be affected, especially in immunocompromised individuals [20]. Most cases of blastomycosis occur in adults, although pediatric cases have also been reported—the diagnostic delay appears to be even more frequent in these patients [23].

Among fungal diseases, blastomycosis appears to have a special predilection for bones [4]. Bone is the third most frequent site where blastomycosis lesions are found, after the lungs and skin [24]. Most of the information available regarding bony blastomycosis comes from a small series of cases. Up to half of the cases of disseminated blastomycosis can show bone involvement. Any bone can be affected, including the vertebrae, ribs, bones of the face and skull, long bones, short bones, pelvic bones and shoulder blades. Patients with blastomycosis osteomyelitis have pain and local edema, which are frequently associated with an ulcer or an adjacent skin abscess.

Furthermore, synovial joint involvement has also been reported. The occurrence of arthritis via direct extension of osteomyelitis acquired from an adjacent focus of infection is well-documented, but cases of arthritis have also been recognized in the context of disseminated disease or as the only form of clinical presentation. Approximately 90% of patients with arthritis due to blastomycosis have extra-articular manifestations at the time of consultation [1, 5]. Arthritis is usually monoarticular, mainly affecting the knee, ankle or elbow. The pain is usually severe and acute, leading patients to consult a physician within a week following onset [5]. Vertebral blastomycosis is frequently associated with epidural, paravertebral or psoas abscesses [18].

Diagnosis

Given that the clinical manifestations of blastomycosis are nonspecific, it is necessary to maintain a high index of suspicion in order to achieve a timely diagnosis. Even in endemic areas, it is common for diagnosis to be delayed [24]. A detailed clinical history should include an individual's place of residence and history of travel to endemic areas, outdoor activities and exposure to plant material as possible risk factors. Immunosuppressed patients are at higher risk of suffering the disease [25, 26]. A history of blastomycosis in a feline or canine pet can also be clinically useful [20, 27]. Serological tests, as well as tests based on immunodiffusion and complement fixation, are not useful in blastomycosis due to their low sensitivities and specificities [20].

The diagnosis of blastomycosis can be made by demonstrating characteristic budding of broad-based, thick-walled

yeast cells upon direct examination of a body fluid (Fig. 22.1). Identification of a neutrophilic infiltrate with non-caseating granulomas in a tissue sample may suggest blastomycosis, and a detailed microscopic examination should subsequently be performed to determine the presence of yeasts of *B. dermatitidis*. In all cases, a microscopic diagnosis should be confirmed by culture to obtain a definitive diagnosis. The cultures require specialized media, and growth can take up to 4 or 5 weeks to be observed [22].

Examining urine samples with a *Blastomyces* cell wall antigen has shown lower diagnostic performance than expected and should not be used to rule out a diagnosis in patients with negative results but clinical suspicion [28]. This test is also not specific since there is cross-reactivity with histoplasma, paracoccidioidomycosis and penicilliosis [22]. Serial measurement appears to be useful for the evaluation of response to treatment or progression of the disease. After the initiation of treatment, an increase in antigenuria can be observed as a reflection of the excretion of dead fungal cells, followed by a progressive decrease in titers as a reflection of successful therapy [28].

There is no typical radiographic pattern of osteoarticular blastomycosis. X-ray may sometimes appear normal. Both long and short bones can be affected in a pattern that can be focal or diffuse. The most common findings are lytic "punched out" lesions and synovial effusions. Up to one-third of patients may show findings consistent with adjacent osteomyelitis [13]. Nuclear magnetic resonance imaging of the spine may show discitis, vertebral body destruction and paraspinal abscesses [29].

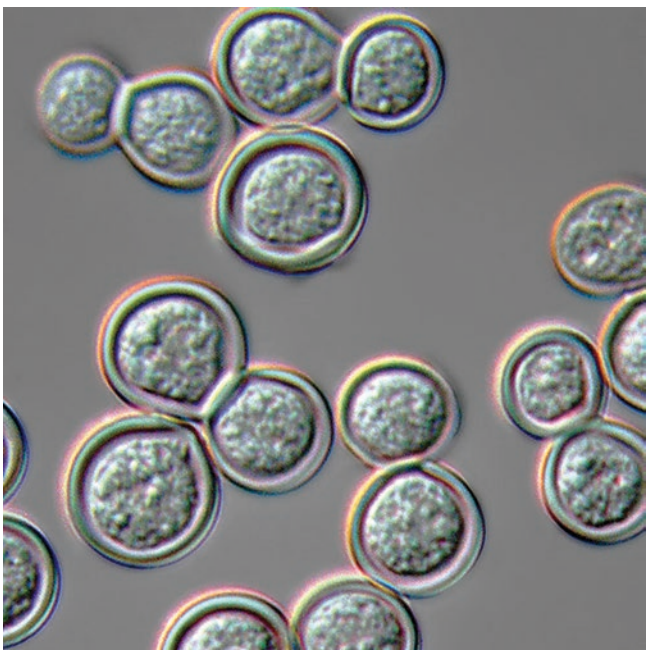

Fig. 22.1 Yeast form of *Blastomyces dermatitidis*. (From Wikimedia Commons. Creative Commons CC0 1.0 Universal Public Domain Dedication)

Treatment

Blastomycosis usually remains localized in the lungs; however, up to 40% of infected persons may develop extrapulmonary infection with cutaneous, osteoarticular, genitourinary or neurological involvement. In an immunocompetent host, pulmonary blastomycosis is usually mild and self-limiting and may not require treatment. However, it is recommended that all infected persons receive treatment to prevent extrapulmonary spread of the disease [20]. All people with moderate to severe pneumonia or disseminated infection or with pre-existing immunodeficiency should receive antifungal therapy [30].

In general, for the treatment of mild to moderate cases, an azole agent—especially itraconazole—may be used for 6–12 months. For cases of severe pulmonary or disseminated disease, central nervous system involvement or in immunocompromised patients, initial treatment with amphotericin B is recommended, followed by itraconazole upon the observation of a satisfactory clinical response [20].

Osteoarticular blastomycosis is more difficult to treat and is more prone to relapse [19, 30]. Patients with osteoarticular blastomycosis should receive a minimum of 12 months of antifungal therapy [30]. Surgery reportedly plays a minor role in the treatment of osteoarticular blastomycosis [19], and there are no specific guides in this regard. Some patients can improve without surgical intervention; however, surgical procedures have been performed in most reports. Therefore, depending on the analysis of each individual case, surgery should be considered (i) for diagnosis through deep tissue sampling, (ii) as a co-adjuvant to antimicrobial therapy by means of draining abscesses or debridement of bone or soft tissues to facilitate the healing of affected areas [1], or (iii) to correct spinal deformities [31].

Prognosis

Osteoarticular blastomycosis requires prolong treatment because it is more difficult to treat and more likely to result in relapse [30]. The infection can spread by means of direct extension from an affected bone to soft tissues and nearby joints, with complications like abscesses and septic arthritis. The progressive destruction of bone can lead to pathological fractures [22]. In one series of 45 patients with blastomycosis of the bone or joints, residual symptoms were reported in 24% of patients; the most frequent symptoms were pain and limited range of joint mobility [1].

Conclusions and Future Directions

Although blastomycosis arthritis is an infrequent clinical manifestation of a relatively rare disease, cases have been reported from many countries around the world. The disease

occurs mainly in individuals who engage in outdoor activities or are exposed to decomposing plant material as well as in individuals with some form of immunosuppression. It is necessary to maintain a high index of clinical suspicion to perform appropriate microbiological testing, avoid delayed diagnoses and initiate timely antimicrobial treatment.

It is expected that advances in basic science techniques, such as sequencing the genome of the microorganism and the identification of as-yet-unknown virulence factors and critical factors for the transition to the yeast phase, will allow advances in molecular diagnostic methods and the development of new medicines with greater specificity and reduced toxicity [32]. Molecular techniques like real-time PCR could provide much more rapid diagnoses from the various available clinical specimens or even from fungal cultures themselves [33]. In spite of several promising reports, it is necessary to carry out additional clinical studies to define the clinical role of new azole agents, such as voriconazole, isavuconazole and posaconazole [34–36].

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