Blastomycosis is a rare fungal infection caused by the thermally dimorphic fungus *Blastomyces dermatitidis*. Study of sporadic cases and outbreaks indicates that the area of endemnicity for *B. dermatitidis* in North America includes the Ohio and Mississippi River basins and the Canadian Provinces and American states that border the Great Lakes. Blastomycosis often presents a diagnostic dilemma, having varied clinical manifestations and involving multiple sites in the body. A thorough travel history and a high index of suspicion are needed when a patient presents with a chronic granulomatous infection of lung, bone, and/or soft tissue. The case that follows and the ensuing discussion highlight the difficulty in establishing the diagnosis of blastomycosis.

**Case Presentation**

A 33-year-old heterosexual Saudi Arabian man studying in Winnipeg, Manitoba, Canada, presented with a 1-month history of a persistent throbbing pain on the anterior-medial aspect of his left distal tibia with radiation to his knee. The pain was associated with progressive swelling, erythema, and calor. The patient denied a history of trauma or past problems affecting the left lower extremity. He denied fevers, chills, or cough, and he did not have a significant medical history. He denied any risk factors for immunocompromising conditions such as infection with the human immunodeficiency virus. All laboratory investigations, including a complete blood count with differential and serum biochemistry, were within normal limits. A nonsteroidal antiinflammatory drug was provided at this time.

Over the ensuing 2 months, the patient noted progression of the pain. Radiographs performed at this time revealed a cystic lytic lesion at the junction of the middle and distal third of the left tibia involving the anterior-medial cortex (Figure 1). A subsequent 3-phase technetium bone scan demonstrated isolated increased uptake in the left tibia corresponding to the lytic area on plain film. A computed axial tomographic scan of the left tibia demonstrated a lytic process involving the same area without peripheral cortical breakthrough; however, periosteal new bone formation with associated soft-tissue edema was present, as consistent with osteomyelitis (Figure 2). A neoplasm was not completely excluded, and therefore the patient consented to a bone biopsy. The bone biopsy was performed though a longitudinal incision of approximately 5 cm in length centered over the lesion. A bone window was created, and the lesion was curetted. The intraoperative specimen demonstrated microorganisms that had the appearance of broad-based budding yeast, compatible with *B. dermatitidis* on histologic examination (Figure 3).

Consultation with a consultant in Infectious Diseases was obtained after the biopsy, approximately 3 months after the symptoms began. At this time, examination revealed a 6 × 4-cm erythematous patch with central....

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fluctuance on the medial aspect of the left midshaft tibia. The chest radiograph did not reveal any pulmonary abnormality. Treatment for *B dermatitidis* osteomyelitis was initiated with itraconazole 200 mg once a day and was continued for 6 months.

In retrospect, a careful travel history revealed that the patient and his family had visited Kenora, Ontario, on 3 separate occasions over the preceding 5 years, the most recent of which was 1 month prior to the onset of symptoms. This geographic area is one of the known endemic regions for *B dermatitidis*. When he visited this region, he stayed in a hotel over the span of a weekend and had limited contact with the outdoors. Most likely this patient developed *B dermatitidis* infection of his left tibia as a consequence of exposure to the endemic area in northwestern Ontario. In follow-up 3 months after completion of therapy the patient was asymptomatic, and a repeat radiograph of the left tibia demonstrated complete resolution of the lytic lesion.

**DISCUSSION**

Blastomycosis is a rare systemic pyogranulomatous disease caused by the thermally dimorphic fungus *B dermatitidis*. In nature, at ambient temperatures, the fungus grows in a mycelial form, whereas at body temperature, the organism grows in its yeast form. Disease caused by *B dermatitidis* occurs most commonly in defined geographic regions, hence its designation as an endemic mycoses. In North America, *B dermatitidis* usually occurs in the central and eastern provinces of Canada (Manitoba and Ontario) and in the United States along the Ohio-Mississippi River Valley areas and the Southeastern, Mid-Atlantic, and upper Midwestern states. *Blastomyces dermatitidis* is also found in Africa, and there have been reports from Israel and Saudi Arabia.

In nature, *B dermatitidis* is presumed to reside in soil, but its exact reservoir is not known. Most epidemics have been associated with waterways and soil that has been largely enriched by organic nitrogen through the excrement of various animals and bird species. The age range of those infected is between 6 months and 78 years of age, and the male-to-female ratio is reported to range from 1.9:1 to 15:1, with African Americans and Aboriginal North Americans affected the most frequently. Outdoor occupations and activities are associated with an increased risk of illness.

It is postulated that initial infection results from inhalation of conidia into the lungs, although primary cutaneous blastomycosis has been reported after direct inoculation from dog bites and in laboratory personnel in a small number of cases. It is suggested that the incubation period ranges from 30 to 45 days; however, a broad range is typically provided for the incubation period because the time of exposure is often unknown.

**The Clinical Presentation and Diagnosis**

Clinical manifestations of blastomycosis are varied and may mimic other disease processes. Typical patterns include asymptomatic pulmonary infection, acute or chronic pneumonia, and disseminated disease involving multiple organ systems. An asymptomatic pulmonary disease occurs in at least 50% of infected people as defined by point-source outbreaks, and the majority of people diagnosed with blastomycosis clinically present with chronic pneumonia. Extrapulmonary spread of infection may occur regardless of the activity of the lung disease, the predominant sites of involvement, in descending order, being the skin, bones, male genitourinary system, and central nervous system. It may be noted that in this patient, the chest radiograph did not demonstrate an obvious pulmonary lesion. Further radiologic investigation of the chest and pelvis was not undertaken because it was not felt to add additional information that would change the type, duration, and outcome of treatment. Bone involvement is discussed in the box on the next page.

**Diagnosis**

A high index of suspicion for *B dermatitidis* osteomyelitis is essential for establishing the diagnosis, for delays often occur because the lesions may go undetected or misdiagnosed for months. The average time span from presentation to diagnosis in 1 series was 7.1 months.

Definitive diagnosis of blastomycosis requires growing *B dermatitidis* from a clinical specimen. Visualization of the characteristic budding yeast form in clinical specimens supports a presumptive diagnosis and usually prompts initiation of antifungal therapy in the appropriate clinical scenario, as occurred in this case. Skin testing and serologic testing lack both sensitivity and specificity and are thus infrequently used to diagnose blastomycosis.

**Treatment**

Treatment guidelines for blastomycosis have been established and depend upon the location and severity of the infection and on host characteristics. In general, spontane-
Bone Involvement in Cases of Blastomycosis

Bone involvement has been reported in 14% to 60% of disseminated cases of blastomycosis. A retrospective review of all cases in the Manitoba and northern Ontario region diagnosed at Health Sciences Center in Winnipeg, Manitoba, Canada, from 1926 to 1988 demonstrated bone lesions as the most common extrapulmonary manifestation in this series, in 24% of cases. Osseous blastomycosis results from hematogenous dissemination or direct invasion from adjacent structures. Common sites of bony involvement in descending order are the vertebrae, skull, ribs, tibia, knee, and tarsal and carpal bones. Osseous sites of involvement are commonly asymptomatic. When long bones are involved, the tendency is for infection to be located in the epiphysis or metaphysis. Blastomyces dermatitidis septic arthritis can be a presenting feature with or without juxta-articular osteomyelitis. Patients with B. dermatitidis osteomyelitis have an average of 2.5 osseous lesions diagnosed on bone scan. Prior to the introduction of effective antifungal therapy, the mortality rate of systemic blastomycosis approached 90%. The radiographic appearance of skeletal lesions is variable and nonspecific; however, 2 basic patterns have been described: a cystic or focal form and a diffuse form. The focal lesions are slowly expanding lytic lesions with sclerotic margins commonly located eccentrically within the metaphysis as demonstrated in Figure 1. The adjacent bone retains its normal architecture and mineralization. Diffuse lesions are rapidly destructive, with a tendency to penetrate the cortex into adjacent joints or to spread to soft tissue and produce fistulae. Sequestra are rarely seen, and periosteal new bone formation is uncommon in both patterns. The radiographic appearance of vertebral lesions is similar to those of tuberculosis. Both infections destroy disc spaces, produce paraspinal masses, erode the vertebral body anteriorly, and skip segments. Differentiation can be difficult except when the infection spreads to adjacent ribs, which is unusual for tuberculosis.

Case reports highlight the variable clinical presentations of skeletal lesions caused by B. dermatitidis. Examples include a lesion mimicking a malignant tumor of the distal radius, an extensive lesion destroying the pelvis with associated draining sinuses and a perirectal abscess, and an abscess of the first metatarsophalangeal joint with underlying osteomyelitis following direct trauma to the area.

The treatment options are amphotericin B, ketoconazole, itraconazole, and fluconazole; however, amphotericin B is the treatment of choice for those who are immunocompromised or have life-threatening or central nervous system disease or for whom treatment with an azole antifungal has failed. For the immunocompetent patient with mild to moderate pulmonary or extrapulmonary disease, azole antifungals are equally effective and less toxic than amphotericin B. In the absence of formal clinical trials, itraconazole is, in the opinion of experts, more efficacious than either ketoconazole or fluconazole and therefore it is the agent of choice; however, ketoconazole and fluconazole are other alternatives. There have been reports suggesting that B. dermatitidis may frequently be an opportunistic pathogen, particularly in persons who are profoundly immunocompromised, such as those in the terminal stages of the acquired immunodeficiency syndrome, organ transplant recipients, or those receiving chemotherapy. In persons who are immunosuppressed, blastomycosis may be a more aggressive condition and is more likely to be fatal than in the immunologically intact host. Frequent relapses of blastomycosis have been observed in persons with acquired immunodeficiency syndrome and in those who continue immunosuppressive therapy, and therefore some have suggested that long-term chronic suppressive therapy with azole antifungal therapy is indicated.

Orthopedic Management

The orthopedic management of B. dermatitidis osteomyelitis includes biopsy of bone lesions for diagnostic purposes, with débridement as necessary. In addition, incision and drainage of abscesses, curettage, and sequestrectomy are required in select cases as adjunctive treatment to antifungal therapy. Splinting and local wound management are also necessary as indicated.

Recommendations

This case serves to illustrate that travelers to endemic areas, even for brief periods, are susceptible to the same endemic infectious diseases as the local residents. The endemicity of blastomycosis has been reported in several areas in North America—specifically, Wisconsin (1.4 cases per 100,000 population) and Mississippi (1.3 cases per 100,000 population)—and in the endemic areas in Canada—specifically, Manitoba (0.62 cases per 100,000 population) and the Kenora, Ontario, district (7.11 cases per 100,000 population). The Kenora, Ontario, district, where our patient likely acquired his disease, has one of the highest rates of blastomycosis reported anywhere in the world. Patients who present with bone lesions and pulmonary disease should prompt the physician to consider B. dermatitidis on the differential diagnosis, particularly if they have had contact with an endemic area. In addition, B. dermatitidis needs to be included in the differential diagnosis of solitary lytic bone lesions.

The authors are familiar with several cases of residents from the endemic area who have presented with manifestations of blastomycosis to care providers outside the
endemic area who were unfamiliar with this condition, resulting in delays in diagnosis and treatment. This has also been reported by others. A thorough travel history and a high index of suspicion for infection with *B. dermatitidis* should lead to the diagnosis. Institution of the appropriate antifungal therapy with surgical intervention as indicated reduces the morbidity associated with this disease and results in rapid resolution of the infection.

**ACKNOWLEDGMENTS**

The authors acknowledge the assistance of the following persons for the completion of this manuscript: Ms. Carolyn Schlippert, Infection Control Unit, Health Sciences Centre, for typing the manuscript; Ms. Assunta Rendina, Health Sciences Centre, Clinical Microbiology Laboratory, for interpretation of histologic slides; Dr. Gerhard Bock, Department of Diagnostic Radiology, Health Sciences Center, for radiologic interpretations; and Dr. K. Baria, Department of Orthopaedic Surgery, Seven Oaks Hospital, Winnipeg, Manitoba, Canada, for his management of the patient.

**AUTHORS’ DISCLOSURE STATEMENT**

The authors report no actual or potential conflicts of interest in relation to this article.

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