The case:

A 41-year-old man presented with bilateral foot pain and a persistent cough 2 months after a camping trip in northern Wisconsin. He had a skin lesion and an abnormal chest radiograph.

Figure: Lateral radiograph of the right calcaneus (A). AP radiograph of the left toes (B).

Your diagnosis?

For answer see page 486
Diagnosis:
Blastomycosis of Bone

Hannah Koh, MD; Terrence C. Demos, MD; Laurie M. Lomasney, MD; J. Paul O’Keefe, MD

The portal of entry for B dermatitidis is the respiratory tract following inhalation of spores (conidia). In soil, the fungus grows as a mold, the mycelial form. Inhaled spores exposed to body temperature convert to budding yeast in alveoli (Figure 2). Yeast forms have a thick wall resistant to phagocytosis, contributing to virulence. After multiplying in the lung, there may be hematogenous spread to other organs. Both cell mediated and antibody responses are well documented, but cell-mediated immunity is critical for control. Foci of infection in lung, skin, or bone result in granulomatous inflammation, but a prominent neutrophilic response is also seen. Involvement in affected organs can be early or delayed.

EPIDEMIOLOGY
The true incidence is unknown because most of those infected are either asymptomatic or have self-limited disease, and in most states the disease is not reportable. States with the greatest number of reported cases are Arkansas, Kentucky, Mississippi, and Wisconsin.

Drs Koh, Demos, and Lomasney are from the Department of Radiology, and Dr O’Keefe is from the Department of Medicine, Chief Infectious Disease Section, Loyola University Medical Center, Maywood, Illinois.
Drs Koh, Demos, Lomasney, and O’Keefe have no relevant financial relationships to disclose.

Correspondence should be addressed to: Terrence C. Demos, MD, Department of Radiology, Loyola University Medical Center, 2160 S First Ave, Maywood, IL 60153 (tdemos@lumc.edu).

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In the United States, most are reported from Ontario, Manitoba, and Africa. Incidence in most endemic areas ranges from 0.5 to 4 cases per 100,000 populations, but is variable within these areas (Figure 3). In Vilas County in northern Wisconsin, annual cases have been as high as 40/100,000, and there have been 3 major outbreaks of blastomycosis. The largest outbreak was reported in 1986, when 48 of 95 young adults attending an environmental camp in Vilas County were infected after exploring and camping near a beaver pond.

The organism grows in warm, moist soil in wooded areas, especially near water. Most cases are sporadic in humans and animals, most often dogs, but focal outbreaks are related to activities where there is wet soil or decaying wood, especially related to forestry work, recreation in wooded areas, and tearing down old buildings. Dog-to-human transmission is rare. Almost all cases are considered to arise from inhalation with initial infection in the lung, even when there is no overt lung disease. Person-to-person transmission is unlikely, but 1 case of sexual transmission from a male with genital urinary infection to his female partner has been reported. The reported male:female ratio is variable, but most recent data indicate only a slightly greater incidence in men. Incubation time is estimated to range from 20 to 100 days (median, 30-45 days).

CLINICAL

Blastomycosis most often involves the lungs. Delayed diagnosis is common due to several factors: blastomycosis is uncommon even in endemic areas, acute presentation is similar to bacterial pneumonia, and chronic disease mimics other diseases, especially pulmonary malignancy and tuberculosis. Extrapulmonary lesions including skin, bone, genitourinary, and central nervous system lesions resemble other more common infections or noninfectious conditions. In 1 study, 90 of 143 (43%) patients had >30-day delay in diagnosis. Overall, up to 25% of patients with blastomycosis have extrapulmonary disease, but the incidence is much greater when multiple organs are involved rather than a single organ. In a series of 56 patients with multiorgan disease, 53 of 56 (91%) had lung disease, 43 (77%) had skin lesions, and 14 (25%) had bone lesions. A large majority of patients with bone lesions have skin or lung involvement or both.

While reported incidence in each organ is highly variable, the relative incidence is consistent: lung is most frequent, followed by skin, bone and joint, genitourinary, and central nervous system lesions.

BONE AND JOINT DISEASE

Bone involvement, the third most common site of blastomycosis after the lungs and skin, is found in up to 25% of patients with multiorgan blastomycosis. Any bone can be involved, but the spine (Figures 4, 5) is most frequent, followed by the pelvis, ribs (Figure 6), and long bones (Figure 7). A majority of patients have a solitary bone lesion. In 1 series of 41 patients with bone lesions, 33 (81%) had a single lesion, 5 (12%) had 2 lesions, and 3 (7%) had ≥3 lesions. In this group of patients, 12 had joint involvement, and 8 had both bone and joint involvement. Joint involvement occurred in 4 patients (12%) when 1 bone was involved but in all 3 (100%) patients with ≥3 bone lesions.

PRESENTATION

A large majority of patients with bone lesions have skin lesions, lung involvement, or both: 42 of 45 (93%) in 1 report. Most patients are symptomatic with pain and swelling due to appendicular lesions and back pain and neurologic symptoms and signs due to spine lesions. However, patients may not have symptoms related to their bone lesion. Spine lesions can lead to paravertebral and psoas abscesses. In the extremities and pelvis, overlying ulcers and soft tissue abscesses can lead to fistulas. Septic arthritis is less common.

Figure 2: Blastomycosis yeast in a human on microscopy with characteristic thick-walled budding mother cell and single equal-size daughter cell. Figure 3: Blastomycosis endemic areas (brown) on satellite view of the United States and Canada. Courtesy of the National Aeronautics and Space Administration (http://visibleearth.nasa.gov). Figure 4: Blastomycosis sacrum MRI of a 22-year-old man with renal transplant, fever, and buttock pain. Diagnosis by culture of a subcutaneous fluid collection. T1-weighted sagittal image showing low-signal fluid collection anterior to low-signal sacral lesion (A). T2-weighted sagittal image showing high-signal of fluid collection and high-signal of sacral lesion (B).
radiologic case study

and is due to direct extension from a bone lesion or hematogenous spread.\textsuperscript{7}

**IMAGING**

Imaging findings of bone lesions are variable, nonspecific, and range from small indolent lesions to extensive aggressive lesions. Bone lesions are often associated with soft tissue involvement and can extend to joints.\textsuperscript{7-14}

**Radiographs**

Hand and foot lesions range from single to multiple well-defined osteolytic lesions, often with sclerotic margins, but can be more aggressive with diffuse, poorly defined bone destruction.\textsuperscript{8,11,12}

Long-bone lesions favor the ends of bones and often appear as well-defined geographic bone destruction with sclerotic margins indicating chronicity but can also have aggressive features. Fungal infection, including blastomycosis, should be suspected when there is substantial associated soft tissue abnormality, including abscesses, sinus tracts, and fistulas, or when there is joint involvement.\textsuperscript{7,11,13,14}

Spine lesions resemble those seen in tuberculosis with extension across intervertebral disks, anterior subligamentous spread with anterior vertebral osteolysis, and sizeable paraspinal soft tissue masses. Vertebral destruction can extend to the pedicles, lamina, and spinous processes. There can be erosion of adjacent ribs, although this type of spread from the spine to ribs seldom occurs with tuberculosis.\textsuperscript{9,11}

**Computed Tomography and Magnetic Resonance Imaging**

Computed tomography and magnetic resonance imaging are most useful for better delineation of pelvic and spine lesions. Computed tomography shows bone destruction and calcifications well and can be used to guide percutaneous biopsies or aspiration of fluid collections.\textsuperscript{8,13} Magnetic resonance imaging is superior for showing soft tissue detail, the spinal canal, and the spinal cord. In general, lesions are low-signal on T1-weighted sequences and high-signal on T2-weighted sequences. Contrast-enhanced scanning can show solid enhancing lesions and peripherally enhancing abscesses and can also be used to assess disease activity after treatment.\textsuperscript{9}

**Nuclear Medicine**

A bone scan with Tc-99m can be used to image the entire body and detect occult lesions.

**DIAGNOSIS**

Serologic tests are both insensitive and nonspecific and are generally not helpful.
A urine antigen assay is commercially available and has demonstrated good sensitivity but frequently cross reacts with other systemic fungal infections. A positive culture is definitive but incubation of up to 2 to 5 weeks may be required. However, prompt microscopic diagnosis can be made by examination for budding yeast either on potassium hydroxide wet mount or on cytologic examination of exudates from skin lesions, bronchoalveolar lavage fluid, sputum, urine, or tissue biopsies of lesions.

**TREATMENT**

Before the availability of antifungal agents, blastomycosis was most often a progressive disease, with mortality as high as 90%. In the late 1960s, Amphotericin B was shown to be effective, but its use was associated with well-known toxicities and adverse reactions. Since the development of the azole antifungal agents in the late 1970s, amphotericin B is rarely used for the entire course of treatment. Itraconazole is currently the azole of choice. Patients with mild to moderate disease are treated for 6 to 12 months, but treatment for 1 year is recommended for those with bone lesions. Amphotericin B is still used as initial therapy for patients with severe disease or central nervous system disease, and for those who are immunocompromised. Once they have stabilized on amphotericin B, itraconazole can be substituted. Some patients with bone and joint disease have undergone surgical procedures including debridement, bone curettage, arthroscopy, rib and sternal resection, and arthroscopic lavage. Overall recovery is good, but patients with advanced disease may have persistent pain, spinal instability, or decreased range of motion.

**CONCLUSION**

Blastomycosis should be considered when a patient with a bone lesion resides in or has visited an endemic area. The imaging characteristics of bone lesions are often nonspecific, but a large majority of patients with blastomycosis of bone also have lung and/or skin lesions. Cultures may not be positive for 2 to 5 weeks, but early diagnosis can be made by microscopic examination of exudates, discharges, sputum, bronchoalveolar lavage, or biopsies.

**REFERENCES**


