Musculoskeletal Coccidioidomycosis
Unusual Sites of Disease in a Nonendemic Area

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Abstract

Coccidioidomycosis is a primary pulmonary infection, endemic to the southwestern United States, caused by inhalation of spores in an immunocompetent host. When systemic spread occurs, the dissemination of infection to musculoskeletal sites might account for 20% to 50% of cases. The musculoskeletal manifestations are well recognized by physicians in endemic areas. We report 2 cases encountered in metropolitan Chicago in which morphologically typical, large, yeast-like, encapsulated, endosporulating organisms were identified in tissue samples and Coccidioides immitis was cultured. One patient had a degenerative-type radiographic picture thought to be related to a sports injury. A second patient with skin lesions and a paraspinal mass required emergency decompressive spinal surgery. A history consistent with exposure to Coccidioides organisms was apparent only for the first patient. Although the diagnosis can be established morphologically by identifying the large endospores in tissue samples, the submission of samples for culture and subsequent microbiologic confirmation requires the diagnosis to be considered clinically. This report emphasizes the rarity of the organism in nonendemic areas and the redundant value of using both morphologic and microbiologic modalities.

Coccidioides immitis is a dimorphic fungus with worldwide distribution but endemic to the arid areas of the southwestern United States, Mexico, and South America. It has been estimated that there are more than 100,000 cases of coccidioidomycosis annually,1,2 although in the absence of an official national case registry, the actual number of cases is unknown. In the United States for 2004, 6,056 cases were reported to the Centers for Disease Control and Prevention, 98% of which were from California and Arizona.3 The appearance of cases in nonendemic areas, in the United States and elsewhere, is rare.4 The ease of international travel emphasizes the need for clinical awareness and diagnostic consideration of this disease, especially in nonendemic areas.1,5

Coccidioidomycosis typically is acquired by inhalation of aerosolized spores or arthroconidia from the soil. The spores develop in the lung into large spherules, ranging from 20 to 200 µm in diameter, which then develop endospores. The saccule containing the endospores may rupture in vivo, whereupon new spherules will develop, or the spores are released to the soil of the external environment to develop into mycelia and future conidia.2 Nonspecific flu-like symptoms develop in only about 40% of patients, and the remainder are asymptomatic. The mechanisms of virulence are not well understood, and the development of disseminated disease is unpredictable but may be suspected with marked elevation of the complement fixation titers. The actual incidence of systemic spread is unknown but is estimated at 1% to 5%1,6 and might correlate with high complement fixation titers. The pattern of clinical infection is analogous to that of tuberculosis, consisting of systemic dissemination from a primary lung focus. Skin, lymph nodes, musculoskeletal sites, and the central nervous system are favored foci of dissemination.
Musculoskeletal involvement is said to be unusual but, according to some authors, might account for 20% to 50% of disseminated cases.\(^1\),\(^2\),\(^7\) Comprehensive reviews of Coccidioides organisms causing osteomyelitis and/or synovitis report higher rates of involvement, which probably reflect the referral nature of the institutions making the reports.\(^1\) The favored sites are the spine and the knee. A previous assertion that monoarticular disease is more common is not supported by one recent review.\(^1\)

Although microbiologic culture is widely regarded as the diagnostic standard and the organism can grow easily within a few days, cultures might not always be submitted. The clinical level of suspicion may be especially low in a patient in a nonendemic area with an extrapulmonary lesion and in whom the pulmonary lesion is inapparent radiographically. Under such circumstances, a fine-needle aspiration\(^8\) or tissue sample will allow morphologic recognition of the large Coccidioides spherule, with or without endosporulation, even in cases of osteomyelitis and joint effusion.\(^9\),\(^10\)

We report 2 cases of musculoskeletal coccidioidomycosis, 1 in the spine and 1 in the ankle. Both patients were from metropolitan Chicago, IL, a nonendemic area for this disease. The diagnoses were established by standard histopathologic examination and supplemented by positive culture results.

**Case Reports**

**Case 1**

A 22-year-old male college student injured his left ankle playing Frisbee approximately 7 months before surgery; he sustained local pain and swelling that were treated conservatively. There were no systemic symptoms. Although he was a primary Chicago area resident, he attended school in Arizona. One month after injury, imaging studies showed a fracture of the medial malleolus with joint effusion, mild ankle swelling, and warmth. Mild pain and swelling persisted, and additional imaging 6 months after the initial injury demonstrated degenerative changes (joint narrowing and subchondral cyst formation) involving the tibiotalar joint.\(^\text{Image 1}\) The erythrocyte sedimentation rate was 6 mm per hour; results of laboratory studies were otherwise normal. Seven months after the injury, the patient underwent a left ankle arthrotomy with synovial biopsy and culture. With the exception of the initial conservative treatment, the major clinical and imaging workup occurred in the Chicago area in the context of ongoing travel between the 2 locations.

Tissue examination showed a chronically inflamed, fibrotic synovium and adjacent soft tissue. Poorly formed granulomas containing large spherules\(^\text{Image 2}\) with focal endosporulation\(^\text{Image 3}\) were identified. Adjacent fragments of cancellous bone also were involved. No necrosis was observed. The culture sample grew C immitis. Some residual ankle discomfort remained even after the patient was treated with fluconazole for 14 months.

**Case 2**

A 53-year-old Chicago female office worker sought care because of progressive bilateral lower extremity weakness and decreased sensation for 1 month. Imaging studies demonstrated a paraspinous mass at the T7-T9 level with destruction of the vertebral bodies and kyphosis at T8. The results of computed tomography of the chest were negative. A plaque-like rash was present over the face and hands, and one of the lesions was
biopsied. A computed tomography–guided biopsy of the paraspinous mass also was done and quickly followed by a decompressive laminectomy to avert impending paralysis. Samples from the skin biopsy and needle aspiration and tissue from the laminectomy showed typical Coccidioides spherules. In the skin biopsy and paraspinous tissue examinations, granulomas were poorly formed and necrosis was rare. The culture was positive for C. immitis. A travel history was not elicited. She was treated with fluconazole and continued to have decreased strength and sensation below the T7 level.

**Discussion**

Disseminated coccidioidomycosis is an unusual complication of an initial primary pulmonary infection in a host who is typically immunologically competent. Infection with Coccidioides organisms requires exposure to a geographically restricted organism not typically transmitted by personal contact. Yet, coccidioidomycosis occurs as well in nonendemic areas, as illustrated by both cases reported herein, and might be related to travel to an endemic region, as illustrated by case 1. Spread of the primary infection might occur, for unknown reasons, in 1% to 5% of cases. Both axial and appendicular (primarily the knee) anatomic sites are involved and might account for 20% to 50% of cases with disseminated involvement.

These often-repeated figures are difficult to verify. In one study, there were 13 musculoskeletal cases of a total of 330 cases reviewed (approximately 4%). Other collections of orthopedic cases, including a literature review, do not indicate a denominator. In one recent review of 223 primary infections confirmed by elevated complement fixation titers, 50 were extrapulmonary and 28 of those (13% of the total and 56% of the systemic cases) were musculoskeletal. Radiographically, the changes are nonspecific, manifesting as destructive bone lesions accompanied by loss of articular cartilage, subchondral bone loss, and synovial thickening, with or without effusion. Although bone lesions are said to be most often monoarticular, multiple organ systems frequently are involved, primarily the skin. In one large series that included 18 cases with cutaneous involvement, 90% also involved other organs, including 6 cases with coexistent bone lesions.

In several studies of bone and joint involvement by Coccidioides organisms, ankle involvement was unusual, observed in 7 of a total of 65 cases; the spine was involved in 22 cases. The ankle was involved in the present case 1 and seems to represent monoarticular involvement. This patient initially was thought to have degenerative arthritis, possibly secondary to a traumatic incident. The degenerative radiographic features notwithstanding, the young age, the unusual location, and the progression of symptoms led to surgical intervention. In case 2, the skin and spine were involved and urgent operative intervention was required to decompress the spine. Lung involvement could not be documented in either case, and both patients were treated systemically. Musculoskeletal disease requires surgical debridement and medical antifungal therapy but still might portend a lifelong risk of recurrence, even if the initial therapy is successful in eradicating the lesion. A historic survey of musculoskeletal cases demonstrated 80% of cases treated successfully with surgery and antifungal therapy, but only 55% success with medical therapy alone.
Whether morphologic examination is superior diagnostically to culture is beyond the scope of this discussion. However, there is value in the redundancy of both methods. Cultures require a level of clinical suspicion and might not always be submitted. Cultures in both present cases, obtained at surgery but reported after the diagnostic tissue examination, also were positive. Fine-needle aspiration and histopathologic examination of surgically obtained samples are high-yield modalities in the diagnosis of Coccidioides infection from any location.\(^8\)\(^-\)\(^10\) The diagnosis in both cases reported herein was established morphologically by observing the typical large, encapsulated spherules with endosporation in a host reaction ranging from diffuse acute inflammation to poorly formed granulomas. These organisms are to be distinguished from the yeast forms of Blastomyces organisms, which are smaller and have broad-based budding, and Cryptococcus organisms, which have an external mucicarmine-positive slime layer. Neither Blastomyces nor Cryptococcus organisms demonstrate endospore formation. The spectrum of the inflammatory reaction is nonspecific but related to the release of spores and the formation of spherules.\(^2\) The absence of a pure, well-formed granulomatous response should not misdirect diagnostic consideration of this deep fungal infection.

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References