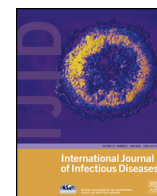


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## Case Report

## Isolated cryptococcal osteomyelitis in an immune-competent host: a case report

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## SUMMARY

*Cryptococcus neoformans* is a ubiquitous organism that often causes opportunistic infections in immune-compromised patients. The pulmonary and central nervous systems are most commonly affected. Osseous involvement is infrequent and is usually associated with disseminated systemic infection. Isolated cryptococcal osteomyelitis is exceedingly rare. We report the case of a 56-year-old immunocompetent man who presented with isolated cryptococcal osteomyelitis of the humerus.

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## 1. Introduction

Cryptococcosis remains an important opportunistic infection, especially in the era of HIV infection in South Africa.<sup>1</sup> Cryptococcosis most commonly affects the lung and central nervous system (CNS).<sup>1</sup> Other sites of infection remain unusual.<sup>1</sup> An unusual presentation of cryptococcal osteomyelitis in an HIV-seronegative man with no other features of immunosuppression is presented.

## 2. Case report

We report the case of a 56-year-old male diagnosed with isolated cryptococcal osteomyelitis of the humerus. He was referred to a tertiary care orthopedic tumor unit 2 months after sustaining a pathological fracture through a lytic lesion of his left humerus. At the time he was employed as a painter on an agricultural farm. The injury was sustained at work when a piece of metal roof sheeting fell directly onto his left arm. He was otherwise well with no previous medical illnesses.

Local staging included radiographs and a magnetic resonance imaging (MRI) scan before histological examination of the lesion. Radiographs revealed an oblique fracture through a lytic lesion in diaphyseal bone at the junction of the middle and distal third of the

left humerus. The lesion appeared purely lytic, geographic, poorly marginated, and had no discernible matrix. Minimal periosteal reaction was present, and the fracture showed signs of early union. The MRI scan demonstrated an ill-defined, irregular medullary lesion, suggestive of an infectious etiology (Figure 1).

Systemic staging included host staging in terms of immune competency and screening for possible primary malignancies and concomitant lesions. An ELISA test for HIV was negative, whilst his serum cryptococcal latex agglutination test (CLAT) was positive. Cerebrospinal fluid examination was normal with both the CLAT and India ink stain negative. He had no clinical features of systemic lupus erythematosus and was found to have a normal glucose level. Serum calcium, prostate-specific antigen, and myeloma screening were normal. Bone scintigraphy showed increased activity in the mid-shaft of the left humerus, with no other bony lesions noted. A chest radiograph and computer tomography (CT) of the chest, abdomen, and pelvis were normal, with no evidence of malignancy or associated lesions.

Whilst undergoing local and systemic staging, a sinus developed on the antero-lateral aspect of his upper arm that drained a non-offensive purulent discharge. Open, incisional biopsy in theatre revealed necrotic tissue and minimal pus. Specimens were taken and sent for histology, bacterial, fungal, and tuberculosis microscopy, culture, and sensitivity. The fracture was clinically united, and no further immobilization was required.

Histological examination showed features of chronic osteomyelitis with no evidence of malignancy. Microbiological investigation confirmed the diagnosis by culture of *Cryptococcus neoformans*

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**Figure 1.** MRI of the left humerus showing an ill-defined, irregular medullary lesion.

using the VITEK2 microbial identification system. The isolate was not genotyped and hence we were unable to distinguish between *Cryptococcus gattii* and *C. neoformans*.

The patient was commenced on amphotericin B at 1 mg/kg/day for his cryptococcal infection. His management was complicated by the development of renal impairment by day 8, despite rehydration with intravenous fluids. The amphotericin B was withheld after 9 days of intravenous therapy and fluconazole 400 mg daily was commenced. His renal function returned to normal within 5 days. He was thereafter recommenced on amphotericin B, but due to a recurrence of renal impairment this was stopped again. A total of 12 days of amphotericin B was administered. Fluconazole 400 mg daily was continued for 10 weeks before the dose was lowered to 200 mg daily. The fluconazole treatment was continued for 6 months and his renal function remains normal.

Repeat radiographs of the fracture site have shown that the fracture has united in an acceptable position and will not require any further surgical intervention.

### 3. Discussion

Cryptococcus is a systemic mycosis caused by an encapsulated 'yeast' fungus and exists as two species: *C. neoformans* and *C. gattii*.<sup>1</sup> *C. neoformans* is prevalent worldwide.<sup>1</sup> It is found in the soil, as well as in avian excreta and is mainly responsible for infection in patients with defective cellular immunity.<sup>1</sup> *C. gattii* was previously believed to be geographically restricted to tropical and subtropical climates.<sup>2</sup> However, in the past decade *C. gattii* has been reported worldwide and has a specialized ecological niche on trees and the hollow of trees.<sup>2</sup> It has been implicated as the cause of infection in immune-competent patients.<sup>1,2</sup>

Cryptococcal infection occurs by inhalation of infected spores or desiccated yeast cells.<sup>1</sup> Infection is usually asymptomatic and may even occur in childhood.<sup>1</sup> During periods of severe cell-mediated immunodeficiency, the organism may enter the circulation, leading to disseminated disease.<sup>1</sup> Clinical manifestations most commonly involve the lung and CNS, although other sites namely the skin, bone marrow, and genitourinary tract may be involved.<sup>1</sup>

Skeletal cryptococcal infections are uncommon, occurring in 5–10% of patients with disseminated disease.<sup>3</sup> Isolated skeletal infections are even less common.<sup>3</sup> Only 47 cases of isolated cryptococcal osteomyelitis in HIV-uninfected patients have been reported between 1974 and 2005.<sup>4</sup> The most common predisposing factors were sarcoidosis, tuberculosis, steroid therapy, lymphoma, leukemia, Hodgkin's disease, and diabetes mellitus.<sup>4</sup>

Skeletal cryptococcal infections may arise due to hematogenous spread from a primary pulmonary source, however direct inoculation through the skin and contiguous spread is also possible.<sup>4</sup> The infection may occur at a single or at multiple sites, with the vertebrae, ribs, tibia, and femur being the most commonly affected.<sup>3–5</sup> The diagnosis is often difficult, as presentation is non-specific; namely soft tissue swelling, bony tenderness, and occasionally fever.<sup>3</sup> The duration of symptoms may persist for up to 33 months prior to diagnosis.<sup>3</sup>

The radiological findings are non-specific, and lesions typically appear purely lytic, with discrete margins and with or without periosteal reactions.<sup>3–5</sup> The differential diagnosis for the radiological features include neoplastic lesions as well as other infections, namely *Staphylococcus aureus*, *Brucella spp.*, *Actinomyces spp.*, and *Mycobacteria spp.*<sup>3</sup> Ultimately, however, the diagnosis of cryptococcosis is made by identification of the organism in the bony lesion.<sup>3–5</sup> This may be from draining sinuses, aspiration, incision and drainage, or open biopsy.<sup>3</sup> Once *Cryptococcus* is identified, disseminated disease should be excluded.<sup>3</sup> Investigations include a chest radiograph, serum examination for antibodies, lumbar puncture for India ink staining, antigen testing and culture, and skin lesion biopsy for microscopy and culture.<sup>3</sup>

Due to the rarity of cryptococcal osteomyelitis there are no specific recommendations regarding the optimal treatment. Surgical debridement reduces infective burden and provides an opportunity to obtain specimens for histological and microbiological examination, and subsequent medical management with antifungal therapy is recommended.<sup>3–5</sup> The Infectious Diseases Society of America does offer treatment recommendations for non-meningeal, non-pulmonary cryptococcosis in HIV-seronegative patients. In cases where cryptococemia or disseminated disease is present, treatment with amphotericin B at 0.7–1 mg/kg/day and flucytosine for 2 weeks is suggested.<sup>6</sup> This is followed by fluconazole at 12 mg/kg/day or 800 mg daily for 8 weeks.<sup>6</sup> Thereafter, the dose of fluconazole should be decreased to 3 mg/kg/day or 200 mg daily and continued for 6–12 months.<sup>6</sup> The response to therapy should be monitored radiologically and followed up, as the infection may relapse and cause chronic infections.<sup>3</sup>

Unfortunately, flucytosine is not available in the public sector in South Africa and only fluconazole 400 mg daily and amphotericin B were available. Furthermore, we were unable to make a distinction between *C. gattii* and *C. neoformans* in this patient.

In conclusion, isolated osteomyelitis is a rare manifestation of cryptococcosis, but should be considered as a differential for lytic osseous lesions, even in the absence of HIV infection. Early intervention ensures prompt diagnosis and treatment and may prevent morbidity and mortality.

**Conflict of interest:** Halima Dawood has received honoraria from MSD-South Africa and Novartis-South Africa for speaking engagements and has received a travel grant from Novartis-South Africa.

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