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Case report

Isolated cryptococcal osteomyelitis as a differential diagnosis of hallux valgus

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Abstract. *Cryptococcus neoformans* is a ubiquitous encapsulated yeast that causes infection as an opportunistic agent primarily in immunocompromised patients, and more rarely, in immunocompetent subjects. Cryptococcal bone involvement can occur in the context of a disseminated infection or as single localization due to, for example, direct inoculation through traumatic injuries or during surgery and minor procedures. Cryptococcosis must be, therefore, included in the differential diagnosis of osteolyic lesions. Bone biopsy should be performed to confirm the diagnosis of cryptococcal infection and to initiate an early course of therapy. Hereby, we present a case of an extrapulmonary isolated cryptococcal osteomyelitis in a female affected with multiple sclerosis (MS), firstly evaluated for hallux valgus, and later diagnosed with a cryptococcal infection by performing a bone biopsy. As there are no codified guidelines on treatment in cryptococcal osteomyelitis we have chosen a combined approach with medical and surgical management with success at 1 year follow-up.

Key words: *Cryptococcus neoformans*, curettage and cementation, hallux valgus, orthopaedics, multiple sclerosis

Introduction

Hallux valgus (HV) is a common foot deformity, estimated to affect 23% of adults and 35.7% of the elderly. (1) It is characterised by the hypermobility and pronation of the first metatarsal ray, which eventually lead to subluxation and pain of the first metatarsophalangeal joint (MTP). HV is not only a prevalent and debilitating condition among the general public, especially women, due to hereditary or improper footwear but also a significant burden on public healthcare with the high demand for foot surgery and its association with foot pain, which can inhibit the level of mobility and physical activity of those who suffer from the deformity. Diagnosis in mainly based on clinical and X-rays of the affected foot.

Cryptococcus neoformans is a ubiquitous encapsulated yeast which, in clinical setting, is most often encountered in patients with profound immunodepression. Primary cryptococcal infection is contracted through inhalation of the pathogen which is present in soils contaminated with avian guano. Subsequently, in patients with defective immune system, hematogenous dissemination to various bodily districts is possible (2). Only less than 10% of patients with cryptococcal disseminated disease present with skeletal involvement (3). Additionally, a direct inoculation through traumatic injuries or during surgery and minor procedures (such as, arthrocentesis or intra-articular corticosteroid injection) is also possible (4). Bone invasion of cryptococcosis is usually characterized by localized osteolytic lesions of any piece of bone in the body, but the most common is the spine (5). Adjacent bones or joints and infected soft tissue can spread continuously. The clinical symptoms and radiological manifestations of skeletal cryptococcosis are nonspecific. Fungal bone

infection can show a wide range of symptoms and onset times, depending on the pathogenicity of the potential organism, the site of infection and the potential health status of the patient. It has been reported that cryptococcal bone infection can lead to subperiosteal new bone formation, periosteal reaction and imaging manifestations of osteomyelitis (6). However, the imaging findings of cryptococcal osteomyelitis usually have no typical features and can also show well-defined osteolytic lesions, similar to malignant tumors. (5,7) Meanwhile, most patients with cryptococcal osteomyelitis show soft tissue swelling and tenderness (6).

Case report

A 62-year-old female presented in an outpatient orthopedics clinic with a one-year history of a progressive left foot pain, recently exacerbated by a trauma at the level of the 1st metatarsophalangeal joint.

The patient had undergone treatment with immunosuppressant medications (azathioprine, interferon, and fingolimod) since 2014 and a prolonged corticosteroid therapy for multiple sclerosis (MS). No history of fever or severe infections in recent years had been reported.

A clinical examination revealed a hallux valgus (Type I – Pigott classification), but did not reveal any palpable lesions. Severe spontaneous pain and tenderness of the 1st MTP joint, associated with already noted paralysis of the left lower limb as a result of the MS, was noted. Clinical examination of the other joints was unremarkable.

Laboratory blood investigations revealed a serum C-reactive protein (CRP) level of 0.66 mg/dL (reference range, 0–0.5 mg/dL) and a total white blood cell count of 6010/mm^3 (reference range, 4000–1100/mm^3) with 55% neutrophils. After an initial evaluation, a foot radiograph and a contrast-enhanced computed tomography scan were executed, which showed an osteolytic lesion with a maximum diameter of 14.5 mm at the distal third of the 1st metatarsal bone (Figure 1). This finding was later confirmed by a magnetic resonance imaging (MRI) (Figure 2). The lesion extended to the subcutaneous tissue, however, there were no signs of hardening or calcification.

An incisional biopsy of the lesion was performed. The histological examination reported stromal bone tissue with intense exudative granulomatous inflammation, with evidence of macrophagic/monocytic intracytoplasmic periodic acid-Schiff (PAS) stain positive microorganisms, compatible with *Cryptococcus neoformans* (Figure 3). The primary cultures resulted negative for microorganisms.

The patient was redirected to an infectious disease consult which excluded the possibility of a

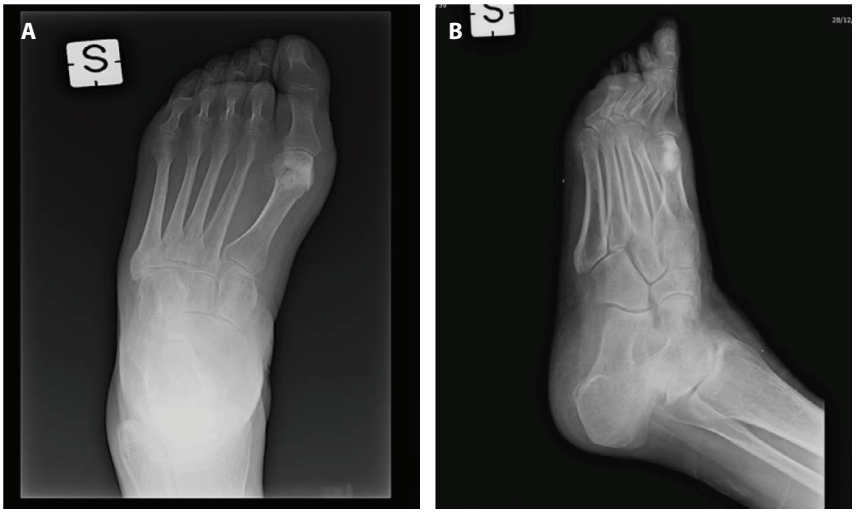

Figure 1. Left foot X-ray (a: anteroposterior view; b: lateral view).

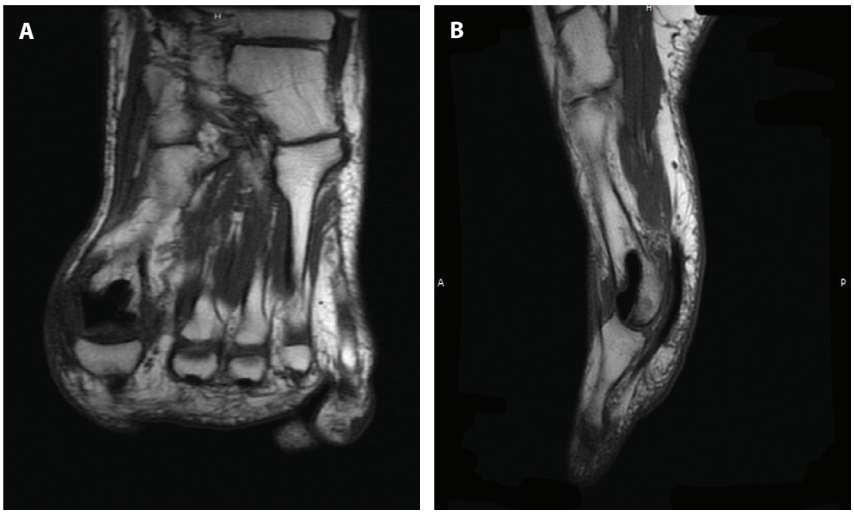

Figure 2. Left foot MRI (a: anteroposterior view; b: lateral view).

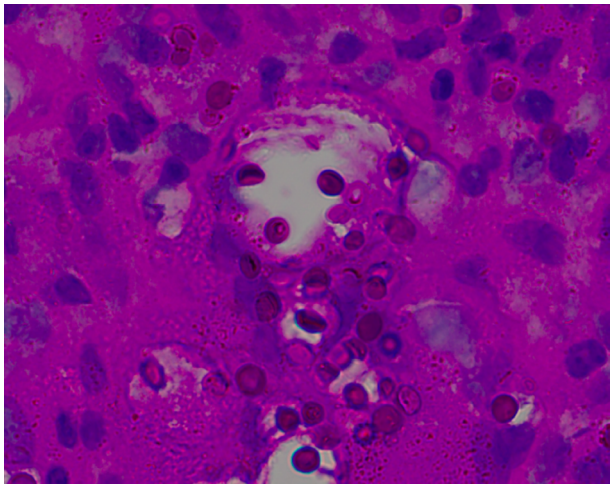

Figure 3. PAS positive microorganisms in bone sample.

disseminated cryptococcal disease through a head and full-body CT scans, ophthalmologic evaluation, and echocardiography. Moreover, the blood cryptococcal antigen and serology tests for hepatitis virus, HIV, *M. tuberculosis* all resulted negative. Fasting blood glucose excluded diabetes and flow cytometry to evaluate T-cell subpopulations did not show any major abnormalities.

A therapy with oral fluconazole (600 mg/day as loading dose, 400 mg/day from the day after) was initiated. A month later, an excisional lesion biopsy, followed by surgical curettage (Figure 4) and cementation, was performed. *Cryptococcus neoformans* was subsequently isolated in the culture from the excised tissue (Figure 5). An antibiogram of the culture confirmed the adequacy of the treatment with fluconazole.

A follow-up of one year post-operative (MRI of the affected foot at 6 months, clinical visit and laboratory exams at 6 months and one year) showed no clinical and radiographic signs of recurrence. Pharmacological therapy with fluconazole was stopped after 6 months of treatment; no change in treatment with immunosuppressants (currently fingolimod and low-dose steroid) was necessary in view of the favorable outcome.

Discussion

An isolated cryptococcal osteomyelitis is a rare entity, and the diagnosis and treatment still remain a challenge (8). Potentially, any skeletal site can be affected and multiple sites can be involved at the same time. Clinical and radiological features are not specific for *Cryptococcus* and may be commonly shared by several conditions, including hallux valgus (as in the case of our patient), rheumatological joint disorders, osteomyelitis due to other infectious etiologies (i.e. other fungi, *Actinomyces*, *mycobacteria*, and *Brucella*) or neoplastic processes. Consequently, as in the presented case, the diagnosis is often the result of a complex

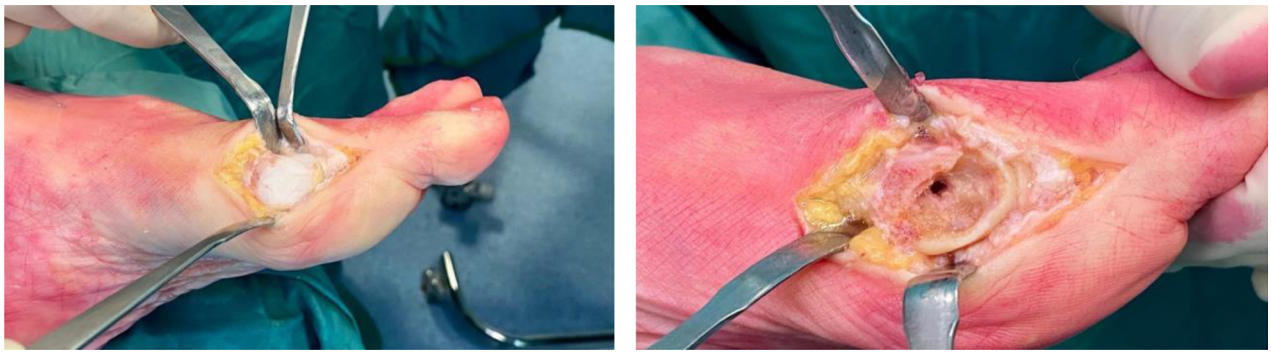

Figure 4. Intra-operative curettage.

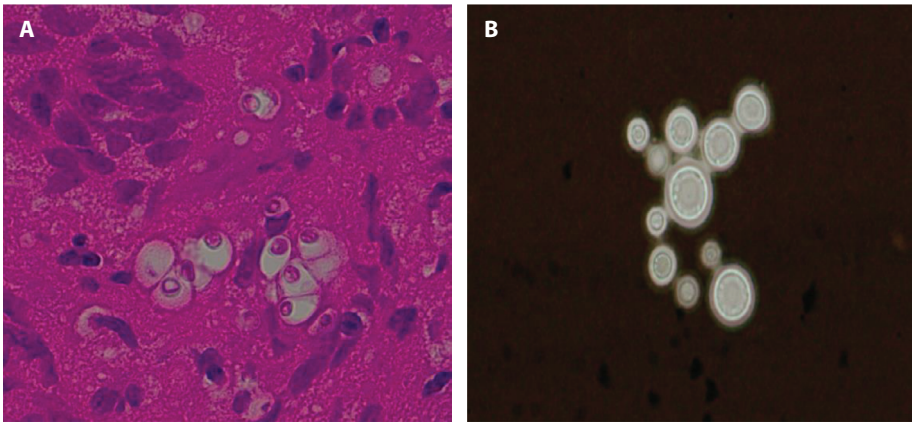

Figure 5. Hematoxylin and eosin stain (Panel a) and India ink stain (Panel b) revealed abundant encapsulated, round yeasts with some budding forms.

clinical and radiological investigation confirmed by a lesion biopsy.

Cryptococcosis may lead to a significant morbidity and mortality since it may become fatal if not treated adequately. The treatment strategy greatly depends on the absence or presence of a disseminated infection (9). Except for the cryptococcal lung and central nervous system infection, there are no other standardized treatment protocols for cryptococcal infection of specific body sites.

A combination of antifungal therapy and surgical debridement has been used to treat most patients with osseous cryptococcosis (6). The primary goals of a surgical intervention are to remove the bony sequestrum and consequently to decrease the infectious burden and to avoid adjacent soft tissue involvement. Given the possibility of dissemination, surgery should be followed by appropriate chemotherapy, usually including amphotericin B, 5-flucytosine and fluconazole as mono- or combined therapy.

In our patient, we opted for treatment with surgical resection and medical therapy with fluconazole, as a single oral antifungal regimen (chosen on the basis of low toxicity, minimal interaction) for the duration of 6 months, based on the laboratory and MRI findings that showed no recurrence of the disease. To reduce the risk of dissemination, the possibility of reducing the dosage of immunosuppressive therapies in patients who use them, must be seriously evaluated in consideration of the risk-benefit ratio for the underlying pathology. In our case, it was not necessary to reduce the immunosuppressive therapy given the favorable clinical outcome of the infection treated with a combined medical and surgical approach.

Conclusion

In summary, we report the first case of an isolated cryptococcal osteomyelitis of the MTP joint in a patient with concomitant MS. Although the imaging findings were atypical, a biopsy and a fungal culture were useful in obtaining a definitive diagnosis. Combined medical and surgical treatment showed to be successful and well-tolerated. However, in order to effectively diagnose and treat patients with an isolated cryptococcal osteomyelitis, clear guidelines should be established.

Since cryptococcal infections are rare and generally subacute, the most important aspect of diagnosing these infections is to include them in differential diagnosis, especially in patients with normal immune function.

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: S.T and T.M drafted the manuscript and followed up with the presented case and collected and sorted the article. S.F and M.F were the senior Infectious Diseases doctors following the case from diagnosis to full recovery and contributed by reviewing the article and help writing the pathogenesis of the germ. The patient was operated by P.P the senior Orthopaedics surgeon on the case which helped by planning methodology to reach a conclusion and intraoperative Images. A.L contributed the microscopic images and definitive diagnosis. All authors meet the 4 criteria based on the ICMJE.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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