Case Report

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Two cases of Osteoarticular Mucor menace: A diagnostic and management conundrum

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Summary **Mucormycosis is an uncommon aggressive fungal infection usually seen in immunocompromised hosts or patients with burns and trauma. The common presentations include rhino-orbital-cerebral and pulmonary involvement. Osteoarticular involvement is a rare presentation of this disease. We present two cases of osteoarticular mucormycosis of pelvis and long bones of the lower limb, one in a patient with burn injury and other one in a patient with chronic granulomatous disease, hitherto a rarely reported association. Delayed diagnosis in a setting where tuberculosis is a common cause of chronic osteomyelitis, challenges in medical and surgical management of these patients are discussed in this report.**

Keywords: Mucormycosis, bone mucormycosis, chronic granulomatous disease

1. Introduction

Mucormycosis is an infection caused by ubiquitous fungi of the order Mucorales and the genera most commonly reported to cause disease includes *Rhizopus*, *Mucor* and *Rhizomucor.* The disease is mostly seen in patients with diabetes mellitus, hematological malignancies, hematopoietic cell and solid organ transplantation, trauma, burns and those on glucocorticoid therapy. This angioinvasive fungal disease can present with varied clinical manifestations, including rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated and miscellaneous forms (*1-3*).

Osteoarticular mucormycosis (excluding extension following rhinosinusitis) is a rare manifestation of this disease. In a systematic review, 34 reported cases were identified between 1978 and 2014 (*4*). We reported a case of long bone mucormycosis and *Mycobacterium abscessus* infection recently (*5*). Mucormycosis can involve bones and joints with the site depending on the mechanism of infection; long bones may be affected after trauma or surgery, or a wide variety of bones may be involved after hematogenous dissemination. Diagnosis is challenging particularly in a setting with rampant tuberculosis. The destructive nature of Mucorales, in addition to the predisposing risk factors presents a formidable challenge in management of these patients. We highlight the above issues in two patients diagnosed with this rare form of the disease.

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2. Case Report

2.1. *Case 1*

A 22-year-old male with no prior comorbidities, apparently well 3 months back, presented with complain of intermittent low-grade fever (documented 100-101° F), associated with continuous dull aching low back pain and weakness of bilateral lower limbs. The weakness was insidious onset, started in left lower limb and gradually progressed to right lower limb over a period of 15 days with bowel and bladder incontinence. He was evaluated at a local hospital, where a magnetic resonance imaging (MRI) of lumbosacral spine with bilateral hip joints was done and category 1 anti-tubercular therapy was initiated with a provisional diagnosis of tubercular sacroiliitis. A month after onset

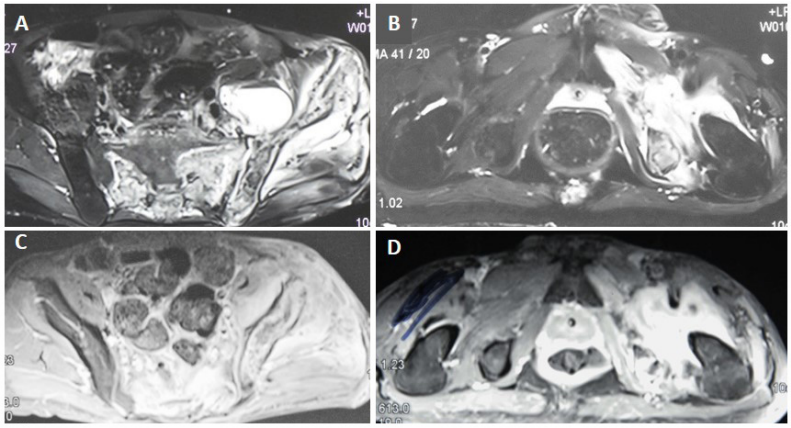

Figure 1. MRI images. Axial fat suppressed T2 images at the level of sacroiliac joints **(A)** and ischial tuberosity **(B)** at the time of admission showing left ilio-psoas collection and bony involvement of the sacrum and left hemipelvis (more on left side and left SI joint). Corresponding images post first debridement **(C,D)** showing mild reduction in the left side collection; however, the sacral involvement appears more extensive.

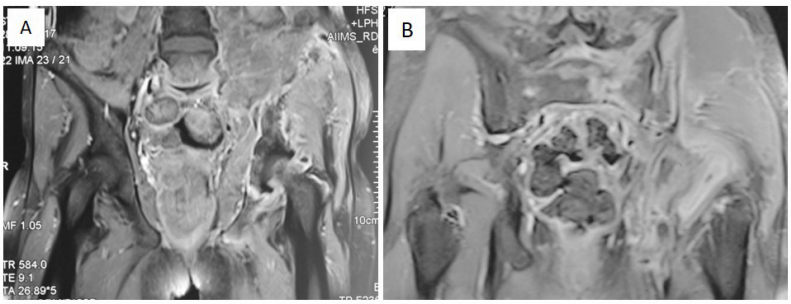

Figure 2. MRI images. Coronal post contrast images at admission **(A)** and follow-up **(B)** showing increased bony involvement and left sided collection.

of fever, he noticed a swelling over the left hip which progressively increased in size and ruptured with black-colored discharge from the wound 10 days later. The area was surgically debrided and histopathological examination was suggestive of aseptate broad hyphae compatible with mucormycosis. He was referred to our institute for further management.

Local examination revealed two ulcers in left gluteal region and left sacral region of size 2 × 3 cm and 3 × 1 cm respectively, with a clean base and granulation tissue. On neurological examination, power grade was 2/5 with deep tendon reflexes absent in left lower limb and mute plantar; power grade was 4/5 in right lower limb. Rest of the general and systemic examination was unremarkable, and vitals were stable. He denied any history of trauma or intramuscular injections.

MRI films were reviewed which revealed left sacroiliitis, left hip arthritis and left psoas collection (Figures 1A, 1B, and 2A). Differentials of a fungal infection (mucormycosis of left pelvic bone), multidrug resistant tuberculosis, non-tubercular mycobacterial infection and chronic bacterial osteomyelitis were considered. Ultrasonography (USG) guided aspiration of gluteal abscess was done, wherein gram stain/culture, fungal stain/culture and GeneXpert were negative. Hematological investigations revealed normocytic normochromic anemia and raised inflammatory markers (Table 1). Liposomal amphotericin B (L-AmB) was initiated at a dose of 10 mg/kg.

MRI was repeated after three weeks of treatment, which did not reveal any improvement, hence caspofungin was added as a rescue therapy. He was evaluated for primary and secondary immunodeficiency which revealed low B and T-cell counts, low neutrophil oxidase activity, feature consistent with chronic granulomatous disease (CGD). A 2-deoxy-2-(^{18}F)fluoro-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scan was performed to determine the disease extent which revealed left paraaortic, prevertebral, common iliac, internal iliac, left external iliac and left inguinal lymph nodes with hepatosplenomegaly. No uptake in liver and spleen was seen.

Meanwhile, he developed drug reaction and leucopenia, secondary to amphotericin, hence it was withheld and later re-started at a lower dose (5 mg/kg). Surgical debridement of pelvis was done, which reconfirmed the diagnosis of mucormycosis (Figure 3). A repeat MRI was done after 4 weeks of surgery revealed worsening in the form of increased left gluteal and iliopsoas collection (Figures 1 C, 1D, and 2B). The collections were drained under USG guidance and

Table 1. Hematological and biochemical profile of the 2 patients

Date	Patient 1/At admission	Patient 1/At discharge	Patient 2/At admission	Patient 2/At discharge
Hb (gm/dL)	8.1	10.3	9.7	8.2
Platelet count (/mm^3)	574 × 10^6	270 × 10^6	2.57 × 10^6	112 × 10^6
TLC (/mm^3)	8,500	5,600	9,000	5,400
Urea (mg/dL)	25	31	25	71
Creatinine (mg/dL)	0.2	1.2	0.4	2.4
Na (mEq/L)	139	134	135	135
K (mEq/L)	3.5	4.4	4.3	3.5
Bilirubin (mg/dL)	0.5	0.4	0.2	0.3
Total protein (g/dL)	6.2	6.4	7.4	6
Albumin (g/dL)	2.7	3.0	3.4	3.8
Globulin (g/dL)	3.5	3.4	4	2.2
SGOT (IU/L)	20	19	17	7
SGPT (IU/L)	19	11	10	6
ALP (IU/L)	322	239	225	236
ESR (mm/hr)	66	52	75	32
CRP (mg/L)	66	20.6	28	16

Hb: Hemoglobin, TLC: Total leukocyte count, Na: Sodium, K: Potassium, SGOT: Aspartate transaminase, SGPT: Alanine transaminase, ALP: Alkaline phosphatase, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein.

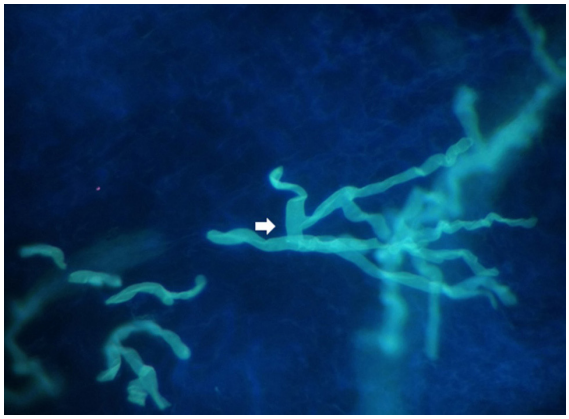

Figure 3. Microscopy findings. Broad aseptate hyphae are observed with right angle branching (arrow) and ribbon like folding under 40x in Calcofluor white-KOH mount indicating mucormycosis.

broad-spectrum antibiotics were initiated to cover for superadded bacterial infection. Due to repeated drug-related toxicities, L-AmB was withheld (total dose 35 grams) and oral posaconazole was initiated. He showed clinical improvement and started ambulating with support. A repeat MRI performed 3 months after surgery revealed partial response.

2.2. *Case 2*

A 40-year-old male, with no prior comorbidities, presented with chronic discharging sinus on the anterior aspect of right leg for 5 months. The sinus developed following debridement performed for burn injury over the leg. He also complained of severe intensity pain in the leg and recurrent episodes of fever (documented 100-101° F) with chills. He was evaluated at a local healthcare facility and diagnosed to have chronic osteomyelitis and referred to our institute. On evaluation, patient was conscious and oriented and vitals were stable. Local examination revealed 10 × 6 cm ulcer present over anterior aspect of lower third of tibia with black eschar with pale granulation tissue with active discharge from the wound. Rest of the general physical and systemic examination was unremarkable. He had anemia and raised inflammatory markers (Table 1).

In view of active discharging sinus, broad-spectrum antibiotics were initiated. A bone biopsy from tibia done outside, was reviewed which showed dead bone trabeculae along with right angle branching broad septate hyphae consistent with mucormycosis. Patient was started on L-AmB at a dose of 5 mg/kg which had to be stopped after second dose in view of deranged renal parameters. Orthopedic opinion was taken and debridement with wash with sinus tract excision with sequestrectomy and saucerization of right tibia was performed. Patient had an uneventful intraoperative and post-operative period and was discharged on oral posaconazole (200 mg QID), due to recurrent acute kidney injury on introduction of L-AmB. A repeat MRI performed 4 weeks after surgery revealed spread of bony lesions to left femur (Figures 4A-4D). The patient was re-admitted, and an above knee amputation was performed after thorough discussion and informed consent. The intraoperative and postoperative events were uneventful. At 2 months follow-up, he was asymptomatic and repeat MRI revealed mild T2/STIR hyperintensity in thigh muscles suggestive of residual disease.

3. Discussion

Osteoarticular mucormycosis is an uncommon manifestation of mucormycosis. In a systematic review of database from 1978 to 2014, only 34 cases were reported (*4*). The review excluded cases of bone

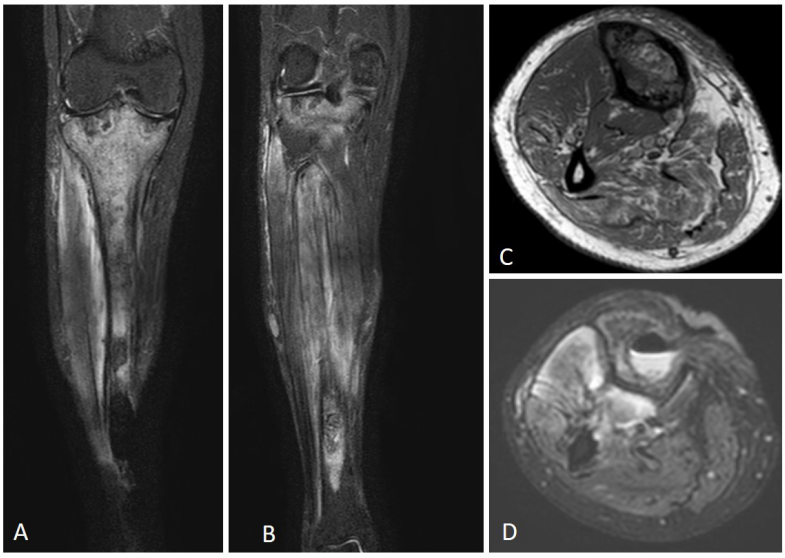

Figure 4. MRI images. (A and B) Fat suppressed T2 coronal images showing extensive marrow signal alteration involving the tibia. **(C)** Axial T1 weighted image showing cortical irregularity and erosions of the tibia. The fibula (*) shows normal marrow and cortical signal. **(D)** Axial fat suppressed T2 weighted image shows an air fluid level within the tibial marrow cavity with sinus tract extending to the skin surface (*). Note also the extensive edema involving the surrounding muscles (arrow).

extension following rhinosinusitis, which is a common site of presentation for mucormycosis. Both our patient had proven mucormycosis as aseptate hyphae was demonstrated in histopathology sections.

Osteoarticular mucormycosis has been reported most frequently after surgical procedures (41%) and trauma (21%); diabetes mellitus (18%) and corticosteroid use (21%) being other significant predisposing factors (*4*). Our second patient had a prior burn injury and underwent surgical procedure; however, the first patient did not have any of the above predisposing conditions. Further, he did not have other source for hematogenous spread of infection, as there was no FDG uptake at any other site on 18F FDG PET-CT scan. His primary immunodeficiency work up revealed low total B and T-cell counts, with low neutrophil oxidase activity (dihydrorhodamine (DHR) assay) suggestive of CGD. Patients with CGD are uniquely susceptible to invasive aspergillosis, but invasive mucormycosis is rare and occurs mostly if patient is receiving corticosteroids (*6*). In a series of 278 patients with CGD, only 5 patients had invasive mucormycosis and all of them were on corticosteroids (*6*). However, neither of our patients received corticosteroids.

The most common presenting features are local symptoms including swelling, tenderness, pain and restriction of movements, while fever is reported in around one-fourth of the patients (*4*). The local features were present in both our patients; fever was present in the first patient since disease onset, while superadded infection was the probable cause of fever in second patient. The reported median diagnostic delay from onset of symptoms is 60 days (*4*). The treatment in our patients was initiated 3 and 5 months respectively, after initial symptoms. Diagnosis of this rare manifestation is challenging in a setting with high burden of tuberculosis, like ours. Biopsy is the mainstay of diagnosis as imaging features are non-specific (*4*).

The cornerstone of management is combined surgical and medical approach. L-AmB is the mainstay of medical therapy and posaconazole is used as maintenance therapy, while debridement (38%) is the most common surgical procedure followed by bone grafting (21%), amputation (15%) and full excision (15%) depending on the site of involvement (*4*). Our first patient had extensive local infiltrative disease, making radical excision a difficult choice and hence, local debridement was opted for. The second patient at presentation had a localized disease and hence, initially a conservative approach with debridement was adopted. However, the rapid spread of disease led to the decision of amputation to preserve the unaffected part of the limb.

The recommended first line of medical therapy for mucormycosis is liposomal or lipid-complex amphotericin B at a minimum dose of 5 mg/kg/day, while posaconazole is recommended as salvage therapy (*7*). The efficacy of L-AmB in mucormycosis is variable across studies depending upon site and extent of involvement, timing of initiation and underlying predisposing conditions. Distinctive immunopathogenesis features contribute to poor response in mucormycosis compared to other invasive fungal infections (*8*). In systematic review of osteoarticular variant of disease, the mortality rate reported was 24% (*4*). Delay in diagnosis may be one of the factors contributing to high failure rates. Management of our patients was further complicated by adverse effects of the drug particularly in the second patient. The drug related nephrotoxicity varies depending on the patient profile, drug dosage

and duration of therapy. In a recent retrospective analysis of 103 treatment courses of L-AMB, 19.4% of patients were classified at risk, 13.6% met an injury classification, and 5.8% were categorized as developing renal failure according to the RIFLE category for renal injury (*9*). Long term L-AmB therapy is associated with more adverse effects (*10*). We discontinued L-AmB in both patients and shifted them to oral posaconazole (800 mg/d). It has been used both in combination with L-AmB and as second line therapy with reported complete and partial response rates of approximately 65% and 7% respectively (*11*). The currently available evidence supports the use of posaconazole as a reserve drug for de-escalation, refractory cases, or patients intolerant to L-AmB (*1,7,12*). The benefit of combination of L-Amb with echinocandin has been reported previously; however, there is insufficient evidence of its efficacy (*13,14*). We used caspofungin in combination with L-AmB as a rescue therapy in the first patient. The two patients have partial response to therapy with clinical resolution of symptoms and improved, albeit persisting radiological findings and are currently on posaconazole. The duration of treatment is not defined and in osteoarticular mucormycosis median time of LAmB use is 45 (5-573) days (*4*).

Osteoarticular mucormycosis is a rare disease and associated with significant morbidity and mortality. Increased awareness will prompt the clinician to suspect this condition in an appropriate setting and attempt early diagnosis by requesting for biopsy with histopathology, staining and culture for fungal etiology. Combined surgical and medical management is the cornerstone for therapy. The duration of antifungals is not defined and it is prudent to continue therapy till there is both clinical and radiological resolution of the disease.

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