CASE REPORT

Cryptococcus neoformans osteomyelitis and intramuscular abscess in a liver transplant patient

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SUMMARY

Cryptococcus neoformans is an important pathogen that can cause severe illness and mortality in immunocompromised patients. We highlight here the case of a 53-year-old man presenting to hospital 4 years postliver transplant with fever, acute renal failure and a medial thigh lesion. Initially treated as bacterial sepsis, the patient failed to improve on broad-spectrum antibiotics. Further investigations revealed disseminated cryptococemia complicated by patellar osteomyelitis and an intramuscular abscess. Unfortunately, although the patient initially showed signs of clinical improvement after starting standard antifungal agents, he deteriorated and died secondary to acute renal failure. Osteomyelitis is a rare manifestation of cryptococcal infection for which there is often a significant delay to diagnosis and treatment. This is the fourth reported case of cryptococcal osteomyelitis in a liver transplant patient and underlines the importance of considering fungal infections in the differential diagnosis of osseous lesions in solid organ transplant and other immunocompromised patients.

BACKGROUND

Cryptococcus neoformans is an encapsulated yeast organism which can cause severe illness or death in immunocompromised patients.¹ It is the third leading cause of fungal infection in solid organ transplant recipients, following aspergillosis and candidiasis, with an overall incidence of 2.8% in this population.^{2–3} Cases most frequently involve the central nervous system or the lungs, but multiple other sites of infection have been documented including the skin, bloodstream,^{2–3} kidneys,⁴ prostate,^{5–6} eyes,⁷ sinuses,⁸ colon⁹ and liver.¹⁰ About 5% of all cryptococcal infections present with osteomyelitis.¹¹ Predisposing factors for cryptococcal osteomyelitis include solid organ transplant, immunosuppressant medication use, diabetes mellitus and HIV.¹¹ We present here an interesting case of cryptococemia in a solid organ transplant recipient manifesting as osteomyelitis and an intramuscular abscess.¹² This rare presentation highlights the importance of considering cryptococcal infection in immunocompromised patients with osseous lesions.

CASE PRESENTATION

The patient is a 53-year-old man who underwent a liver transplant in 2012. His underlying disease was hepatitis C-related cirrhosis. He was on an immunosuppressive regimen including prednisone and tacrolimus and did not have any history of graft

rejection. His medical history was otherwise relevant for insulin-dependent type II diabetes, chronic kidney disease with baseline creatinine 180 µmol/L and chronic gastritis with oesophageal varices.

The patient was initially seen in a community hospital complaining of severe pressure headaches, emesis and a 1 month history of progressive left knee pain. On admission, the patient appeared septic and was in acute renal failure, with a creatinine of 252 µmol/L. He had severe pancytopenia (maximum platelet count $72 \times 10^9/L$) and required four transfusions. He did not display any mental status changes. A secondary survey revealed a pruritic ulcerated lesion on his medial thigh as well as severe left knee pain. There was no history of trauma to the area.

INVESTIGATIONS

The initial MRI of his head showed an area of abnormal enhancement in the left frontoparietal area, as well as a small cystic lesion in the posterior frontal gyrus (figure 1). A chest X-ray revealed no consolidations or pleural effusions, but a CT thorax showed one small non-specific pulmonary nodule. Initial blood cultures did not grow any organisms and the patient was placed on an empiric broad-spectrum antibiotic regimen including intravenous ceftriaxone, metronidazole and vancomycin for suspected bacterial sepsis in the setting of multiple skin lesions. A lumbar puncture was not performed, as it was initially considered a high-risk procedure due to his thrombocytopenia. There were also concerns about possible mass effect from the lesion causing raised intracranial pressure.

His ulcer and knee pain failed to improve on this therapy and he continued to have intermittent fevers. One month after admission, repeat blood cultures showed growth of undifferentiated yeast organisms. Subsequently, he was transferred to a larger tertiary care facility for further investigations and treatment.

New blood cultures incubated on brain heart infusion agar and non-selective sheep blood agar grew *C. neoformans* and cryptococcal serum antigen titres were positive (1:512) using the Meridian Bioscience Cryptococcal Antigen Latex Agglutination System. A white blood cell scan of his left leg showed intense uptake in the left patella consistent with lytic destruction and osteomyelitis, and there was significant white blood cell accumulation in the distal left quadriceps suggestive of an intramuscular abscess (figure 2). The abscess was drained and the purulent material was sent to the Ontario Public

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Figure 1 Area of abnormal leptomeningeal enhancement of the left posterior frontal/parietal lobe with a small cystic cavity (7–8 mm) in the posterior frontal gyrus.

Health Lab for speciation confirmation and sensitivities. Total time delay to diagnosis and initiation of appropriate antifungal therapy was 46 days from the patient's initial presentation.

A repeat head MRI was done 3 days following initiation of appropriate antifungal therapy and demonstrated a reduction in the size of his brain lesions.

DIFFERENTIAL DIAGNOSIS

An ulcerated skin lesion with joint pain and intermittent fevers could represent a number of infectious or non-infectious causes. Although this presentation is consistent in appearance and symptomatology with bacterial osteomyelitis, it is important to also consider opportunistic infections or tuberculosis in immunocompromised populations.^{2 13} Exposure history is an important consideration to rule out lesions caused by endemic mycoses, including coccidioidomycosis, blastomycosis and histoplasmosis.¹³ The appearance of a lytic bone lesion on imaging can also suggest a malignant aetiology, particularly in patients with a history of prostate or lung cancer.^{11 13} The

Figure 2 Diffuse white blood cell accumulation in the quadriceps group suggestive of intramuscular abscess. Intense uptake in the left patella corresponding to lytic destruction consistent with osteomyelitis.

clinical picture and laboratory tests can often be non-specific, and as such, delayed diagnosis and treatment remain important concerns.

TREATMENT

The intramuscular abscess was drained and the patient was started on induction therapy with flucytosine 100 mg/kg/day and liposomal amphotericin B (AMB) 3 mg/kg/day. His prednisone and tacrolimus were withheld. He remained afebrile and his vital signs were within normal limits. His blood cultures were negative by day 10 of antifungal therapy and he was transferred back to his local community hospital for completion of therapy.

After 14 total days of liposomal amphotericin B and flucytosine treatment, the patient was stepped down to a consolidation regimen of fluconazole 800 mg/day, which he was to continue for 2 months, followed by a prolonged maintenance phase with fluconazole 200 mg/day for 6 to 12 months.

OUTCOME AND FOLLOW-UP

The patient initially improved clinically when the appropriate treatment was given, and he was transferred back to his local community hospital to complete therapy. However, despite being given a lower dose of AMB due to concerns about his chronic renal injury, the patient's creatinine began to rise during the induction phase of his antifungal treatment. His liver enzymes also began to rise, at which time his tacrolimus was resumed to prevent loss of graft function.

Unfortunately he did not respond well to this treatment. His renal failure progressed rapidly, and he became intermittently febrile with fluctuating levels of consciousness. He refused his oral antifungal medications on some days and declined further investigations. As the patient's renal function continued to decline, he became increasingly confused and began having severe electrolyte disturbances, which were managed medically. His prognosis with regards to his clinical status and multiple comorbidities were discussed with his power of attorney, who stated that aggressive resuscitation efforts and haemodialysis were not within the patient's goals of care as per his previously stated wishes. The patient himself was no longer able to participate in the discussion at that time.

Invasive treatment was not pursued and comfort measures were initiated. The patient died after 33 total days of antifungal therapy. Although there was some laboratory evidence of loss of graft function, a liver biopsy was not performed in accordance with the family's wishes.

DISCUSSION

C. neoformans infection in solid organ transplant patients most frequently occurs in the late post-transplant period, often between 16 and 21 months.¹⁴ It can be due to reactivation of a pre-existing host colonisation or can represent primary infection after new exposure.^{2 15} The majority of patients have some degree of neurological involvement on initial presentation, most commonly meningitis, with fever and constitutional symptoms. Pulmonary involvement is also common.² Lesions have also been described in the brain, lungs, skin, bloodstream,^{2 3} kidneys,⁴ prostate,^{5 6} eyes,⁷ sinuses,⁸ colon,⁹ liver¹⁰ and blood vessels as vasculitis.¹⁶

Bone involvement occurs in only 5% of cases, and most often affects the lumbar spine or lower extremities.¹⁷ Cryptococcal osteomyelitis generally represents haematogenous spread from a primary source, but cases of isolated osteomyelitis due to direct inoculation have been reported.¹¹

Table 1 Cryptococcal osteomyelitis case summaries highlighting differences in presentation, delay to diagnosis and patient outcome in solid organ transplant recipients

Case (reference)	Case summary	Mode of diagnosis	Delay to diagnosis	Affected organs	Abscess formation	Immunosuppressant dose modification	Outcome
1 (Current case)	53, male, headaches, renal failure, painful L thigh ulceration and progressive L knee pain 4 years following liver transplant	MRI head; leg X-ray, WBC scan; serum cryptococcal Ag titre (1:512); abscess fluid culture	46 days	Disseminated: bone (L patella), overlying skin and soft tissue, CNS, blood	Present	Discontinued	Died secondary to renal failure
2 ¹¹	55, male, painful R tibia lesion 17 months following liver transplant	Leg X-ray, serum cryptococcal Ag titre (1:4), bone biopsy and tissue cultures	Unspecified	Disseminated: bone (R tibia), overlying skin and soft tissue, CNS, blood, lungs	Absent	Unspecified	Full recovery with antifungal therapy + surgical debridement
3 ¹²	66, male, weight loss and painful L thigh mass 6 years following liver transplant	Bone scan; tissue cultures; serum cryptococcal Ag (1:32)	Unspecified	Localised: bone (L fibula), overlying skin and soft tissue	Present	Decreased tacrolimus to 1 mg TID	Full recovery with antifungal therapy only
4 ¹³	36, male, headaches and scalp mass 2 years following liver transplant	MRI head; lesion biopsy mass spectrometry	14 weeks	Localised: bone (R frontal skull), overlying scalp	Present	Unspecified	Full recovery with antifungal therapy+surgical debridement

CNS, central nervous system; L, left; R, right; WBC, white blood cell.

A literature review was performed by searching PubMed and Medline Ovid for articles containing the terms 'Cryptococcus' and 'osteomyelitis'. Articles describing transplant patients were included, while articles describing patients with other predisposing conditions such as sarcoidosis or HIV were excluded. Reports describing cryptococcal osteomyelitis in immunocompetent patients were also excluded and duplicate articles were removed. To our knowledge, including this case, only four reports of cryptococcal osteomyelitis in solid organ transplant recipients have been described to date, as summarised in table 1.

For solid organ transplant recipients with evidence of meningeal disease, the Infectious Diseases Society of America (IDSA) recommends a three-stage treatment regimen. This begins with an induction phase consisting of liposomal AMB (3–5 mg/kg/day) or Abelcet (5 mg/kg/day) and flucytosine (100 mg/kg/day) for at least 2 weeks.^{18 19} This can be extended if the infection is refractory to treatment. However, it is important to closely monitor the patient for nephrotoxicity during the course of this treatment, as it is a common side effect of AMB.^{3 18} The induction phase is followed by a consolidation phase consisting of fluconazole 400–800 mg/day for 8 weeks.^{18 19} Finally, it is recommended that the patient undergoes a period of prolonged maintenance using lower dose fluconazole at 200–400 mg/day for 6 to 12 months.² Renal function must continue to be closely monitored with all antifungal therapy in organ transplant recipients and, when possible, it is recommended that immunosuppressive medication be tapered down during acute infection.^{3 18} In the absence of central nervous system infection, the use of an all-oral regimen has been reported but has not been studied extensively.¹³

We presented here a case of cryptococcal osteomyelitis with an intramuscular abscess in a solid organ transplant recipient. Although the patient was managed as per the IDSA guidelines once the diagnosis was established, there was a significant time delay between initial presentation and diagnosis. Due to the relatively rare incidence and non-specific clinical and radiological picture, *C. neoformans* is not always considered a possible pathogenic agent in bone lesions. However, delayed diagnosis and treatment can have a significant impact on morbidity and mortality. This case stresses the importance of considering cryptococcal infection in the post-transplant patient presenting with multiorgan infectious symptoms including brain, bone and soft tissue lesions, as well as the importance of closely monitoring renal function with antifungal therapy in this population.

Learning points

- ▶ Cryptococcal infection in solid organ transplant patients generally presents with meningitis and pulmonary lesions.
- ▶ Extracranial and extrapulmonary manifestations of disseminated cryptococcosis are relatively rare, with osteomyelitis present in 5% of cases.
- ▶ Antifungal therapy using a liposomal amphotericin B and flucytosine initial therapy followed by long-term fluconazole maintenance phase has been well established.
- ▶ Delay in diagnosis (in the absence of expected classic presentation/symptoms) can lead to increased morbidity and mortality.

Contributors SMP collected information pertaining to the case and completed initial draft of manuscript. She also reviewed the medical literature. RR edited the draft and verified the literature review. SMH was Infectious Diseases consultant who started the treatment and continued follow-up. He reviewed and revised several drafts of the manuscript.

Competing interests None declared.

Patient consent Obtained.

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