Case report

Axillary lymphadenopathy in a liver transplant recipient: Initial manifestation of disseminated cryptococcosis

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Abstract

Immunocompromised patients, especially organ transplant recipients, are at risk for opportunistic infections. Cryptococcus, a ubiquitous environmental fungus, can cause potentially fatal infection in such hosts. While it can involve any organ in the human body, respiratory and central nervous systems are commonly affected. We present a case of disseminated cryptococcal infection in a liver transplant recipient in whom the initial presentation was bilateral axillary lymphadenopathy, a relatively rare clinical manifestation. Rapid diagnosis and initiation of appropriate antimicrobial therapy are paramount for favorable clinical outcomes, particularly in this patient population.

Introduction

Cryptococcus is a ubiquitous environmental yeast [1]. The incidence of cryptococcosis has risen recently given a relative increase in the immunocompromised patient population such as the organ transplant recipients [1]. Clinical manifestations are diverse, though common sites of infection are the respiratory and central nervous systems [1]. Rapid diagnosis and initiation of appropriate antimicrobial therapy is important for favorable outcomes [1].

Case

A 74-year-old retired man with history of orthotopic liver transplantation 4 months prior, presented with malaise, 20 pound weight loss, and 1–2 months of diminished appetite. He denied fever, cough, chest pain, shortness of breath, rash, headache, or abdominal symptoms. The patient had resided in Vietnam for a year in the remote past and worked in construction for about 50 years. His past medical history included coronary artery disease, hypertension, and chronic renal failure. Surgical history was significant for cholecystectomy that was unfortunately complicated by injury to the common bile duct and hepatic artery, warranting liver transplantation. There were no episodes of hepatic graft rejection. He denied sick contacts or recent travel. Immunosuppressive medications were tacrolimus and mycophenolate mofetil; opportunistic infection prophylaxis included trimethoprim-sulfamethoxazole and valganciclovir.

On examination, the patient was afebrile and hemodynamically stable. His oxygen saturation was 98% on room air; he was awake, alert, and oriented. Physical examination revealed bilateral non-tender, non-matted axillary lymph nodes and a well-healed abdominal surgical scar. The remainder of the examination was essentially unremarkable. Laboratory evaluation was notable for a white blood cell count of 1560 / μL (4400–11,300 / μL) with an absolute neutrophil count of 420 / μL (2000–9300 / μL). Atypical lymphocytes were elevated at 16% (0–10%). Serum creatinine was 2.67 mg/dL and AST, ALT, and serum bilirubin were within normal limits. Non-contrast CT of the chest, abdomen, and pelvis revealed extensive lymphadenopathy including enlarged bilateral axillary lymph nodes, measuring 1.5 × 1.2 cm on the right and 1.2 × 0.5 cm on the left, and multiple enlarged mediastinal lymph nodes, largest in the pre-carinal region measuring approximately 1.7 × 2.3 cm. Two pulmonary nodules were seen in right upper lobe with cluster tree-in-bud opacities. Additionally, a 6.2 × 5 cm fluid collection around the hepatoportal fossa was evident.

A right axillary lymph node excisional biopsy was performed. Microscopic images of the surgical pathology specimen are shown under different staining techniques (Figs. 1–5). H&E-stained sections demonstrated cleared-out spaces containing pleomorphic refractile round to ovoid cells, occasionally demonstrating narrow-based budding (Figs. 1 and 2). The cells were positive with Periodic acid-
Schiff (PAS) and Grocott’s methenamine silver (GMS) stains, which stained the organisms magenta and black, respectively (Figs. 3 and 4). Mucicarmine highlighted the thick mucopolysaccharide capsule red (Fig. 5). This stain is specific for *Cryptococcus* species and helps differentiate from the other nonencapsulated yeast-like fungal organisms [2]. Flow cytometry did not reveal immunophenotypic findings indicative of lymphoma.

The findings above established the diagnosis of cryptococcal infection in our patient. Additionally, serum cryptococcal antigen was positive, 1:8192 (normal < 1:1) and blood cultures grew *Cryptococcus neoformans*. Lumbar puncture was done that showed 3 nucleated cells per μL, normal glucose, but elevated protein to 58 mg/dL. CSF cryptococcal antigen was positive to 1:32 (normal < 1:1). The abdominal collection was drained percutaneously; fluid cultures also grew *Cryptococcus*, suggestive of peritoneal abscess. The diagnosis of disseminated cryptococcosis was made.

An initial 2 week induction therapy with liposomal amphotericin B and flucytosine was initiated that the patient tolerated without any adverse effects. This was then transitioned to consolidative

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**Fig. 1.** H&E stain: The section shows lymphoid tissue admixed with adipose tissue with diffuse involvement by encapsulated fungal yeast forms/organisms. The organisms are surrounded by ‘cystic’ spaces enclosed by fibrosis (solid arrows highlight the fungal yeast forms/organisms with surrounding ‘cystic’ spaces). There is an associated non-necrotizing granulomatous inflammation (open arrows highlight the focal granulomatous inflammation).

**Fig. 2.** H&E stain: The fungal yeast forms/organisms are characterized by clear, concentric spaces with a thick capsule (the solid arrow points out one of the organisms with a prominent thick capsule). The organisms have a characteristic narrow based budding (indicated by the open arrow).

**Fig. 3.** Periodic acid–Schiff (PAS) stain highlights the yeast forms/organisms by staining a magenta color. The open arrow indicates the characteristic narrow based budding associated with *Cryptococcus*, and the black arrow pointing at the capsular material. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

**Fig. 4.** The Grocott’s methenamine silver (GMS) stain highlights the yeast forms/organisms by staining the cell walls black.

**Fig. 5.** The mucicarmine stain highlights the fungal yeast forms/organisms by staining the thick mucopolysaccharide capsule red.
phase for 8 weeks and subsequently to the maintenance phase with oral fluconazole. A repeat CT scan was done 8 months after the initial presentation that revealed overall decrease in mediastinal and axillary lymphadenopathy as well as reduction in size of the intraabdominal fluid collection. The patient remains on suppressive antifungal therapy and doing relatively well a year from the initial diagnosis of disseminated cryptococcosis.

**Discussion**

The differential diagnosis for lymphadenopathy in this patient was broad and included fungal, bacterial, and mycobacterial infectious, as well as hematological malignancies such as post-transplant lymphoproliferative disorder (PTLD). The patient’s occupational history of several years in construction raised concern for mycoses such as blastomycosis, cryptococcosis, coccidioidomycosis, and histoplasmosis, particularly in this immunocompromised host. Prior time spent in Vietnam also raised the possibility of melioidosis. Mycobacterial infections such as tuberculosis were also considered.

Lymphadenopathy was a prominent clinical and radiological sign in our patient. Although Cryptococcus can infect any organ, brain and lung are the most commonly involved [1]. Rarely, the initial manifestation may be lymphadenopathy alone; this presentation has been reported in both immunocompromised and immunocompetent hosts [3,4]. While fine needle aspiration cytology (FNAC) may be the initial diagnostic modality in some patients, excisional biopsy may be preferred if lymphoma is suspected [5].

Different histopathological features have been described with cryptococcal lymphadenitis, including presence of granulomas, epithelioid cells and necrosis [6]. In advanced immunosuppressive states such as in AIDS patients, granulomas may be minimal. This has been attributed to low CD 4 counts [6]. Tuberculous lymphadenitis, also characterized by necrotizing granulomas, should be considered in such clinical scenarios, especially in areas where TB is prevalent. Tissue diagnosis with appropriate staining and culture techniques will be needed to differentiate these entities [6].

Chronic fungal infections may manifest in unusual and atypical clinical presentations. A high degree of suspicion is important in immunocompromised hosts such as organ transplant recipients. Early diagnostic modality such as obtaining tissue for rapid diagnosis is paramount to institute pathogen directed therapy in this patient population for favorable outcomes.

**CRediT authorship contribution statement**

All the authors have contributed to the writing of the manuscript of the case report.

**Funding**

No funding applicable to this article.

**Consent**

Not applicable. We have ensured to not report any potential identifying information in the manuscript.

**Conflict of interest**

None of the authors have any potential conflict of interest to disclose.

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