IDCases 29 (2022) e01571

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Pulmonary tuberculosis and Cryptococcal native knee septic arthritis with osteomyelitis in an immunocompetent patient: Mycobacterial effect on CD4 function and cellular immunity

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ARTICLE INFO

Keywords:
Coinfection
Cryptococcosis
Tuberculosis
Immunocompetent
Lymphopenia

ABSTRACT

Clinically significant cryptococcal disease is typically seen in patients with human immunodeficiency virus (HIV). However, Cryptococcosis has also been observed among non-HIV immunocompromised hosts. Cryptococcosis and tuberculosis (TB) infections both occur due to impaired cell mediated immunity but co-infection is rare among immunocompromised patients. Co-infection of these pathogens is even less reported in immunocompetent hosts. We present a case of Cryptococcal left native knee septic arthritis with tibial osteomyelitis in an HIV negative patient with recently active tuberculosis.

Introduction

Cryptococcus is an encapsulated heterobasidiomycetous fungi that commonly causes extensive disease in patients with human immunodeficiency virus (HIV). *Cryptococcus neoformans*, the most common cause of human cryptococcal infection, was first isolated in nature from peach juice in 1895. Since the AIDS epidemic, the prevalence of cryptococcosis has increased. At least 10 % of patients with AIDS in the United States are afflicted by cryptococcosis [1].

However, Cryptococcosis has also been observed in HIV negative hosts. Some studies indicate that 10–40 % of HIV negative patients with cryptococcosis have no apparent immune deficiency [2]. However, these patients commonly have underlying conditions affecting CD4 T-lymphocyte cell-mediated immunity, a major mechanism in defense against *Cryptococcus*. These conditions include organ transplantation, cirrhosis, peritoneal dialysis, advanced malignancy, or prolonged corticosteroids treatment [3]. Infection with TB is associated with lymphopenia and may represent an important risk factor for cryptococcal co-infection.

Objective

The purpose of this case is to demonstrate the clinical importance of TB induced lymphopenia in an HIV negative patient with Cryptococcal native knee septic arthritis and osteomyelitis.

Case report

36-year-old Micronesian male presented with worsening left knee pain and swelling over the last seven days. His past medical history includes iron deficiency, chronic hepatitis B, and recently active TB. He described a throbbing pain encompassing his entire left knee. Additionally, he endorsed fatigue and night sweats without fevers, cough, or dyspnea. There is no personal or family history of immune deficiency. Seven months prior he was admitted to an outside facility due to left sided pyelonephritis and was found to have an abnormal CXR. Bronchoscopy and bronchial culture were positive for pansusceptible *Mycobacterium tuberculosis*. Fluid drained from his left chest wall abscess also grew *Mycobacterium tuberculosis*. At that time, urine acid-fast bacilli (AFB) stain was positive, and a left ureteral stent was placed for presumed TB-related pyelonephritis. However, urine *Mycobacterium tuberculosis* PCR was not performed. He was started on a four drug intensive phase regimen under direct supervision which he completed for two months. Currently, he takes isoniazid and rifampin for TB continuation phase along with Vitamin B6.

Physical exam revealed a warm, tender, erythematous left knee. Knee flexion was severely limited due to pain and he was unable to bear weight on his left leg. Pulmonary exam demonstrated normal lung sounds with symmetric chest rise. The remainder of the exam was unremarkable. Joint arthrocentesis produced bloody synovial fluid containing 8559 white blood cells without crystals. Subsequent cultures of

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https://doi.org/10.1016/j.idcr.2022.e01571
Received 21 March 2022; Received in revised form 9 July 2022; Accepted 11 July 2022
Available online 14 July 2022

this fluid yielded *Cryptococcus*. Magnetic resonance imaging (MRI) of his left knee, seen in Fig. 1, suggested infectious arthritis. Fungal cultures of his blood and cerebral spinal fluid were negative although serum Cryptococcal antigen was positive. During this admission, immunodeficiency work up revealed reduced levels of CD3(431 cells/mcl), CD4 (269 cells/mcl), and CD8 (142 cells/mcl) T cells. HIV infection was ruled out with fourth-generation antibody/antigen combo testing at an outside hospital and at our institution. HIV 1 PCR was not requested.

Oral fluconazole was started and he underwent a left knee irrigation and drainage, synovectomy, and arthroplasty. Fig. 2 shows an intraoperative picture. A spacer was placed using amphotericin B and vancomycin cement. Intraoperative tibia samples obtained grew *Cryptococcus* as well.

Discussion

Cryptococcus neoformans is an encapsulated fungus that is distributed worldwide. It is typically found in soil, decaying wood, tree hollows, or the excreta of pigeons, cockatoos, and canaries [4,5]. Additionally, its major portal of entry is through inhalation of environmental propagules from soil or bird droppings [6]. Clinical manifestations of *C. neoformans* are variable and range from asymptomatic colonization to life-threatening disease. The central nervous system and lungs are the most common infection sites. Because the natural defense against *Cryptococcus* is mediated by CD4 Lymphocytes, it commonly infects those diagnosed with AIDS [7].

Mycobacterium tuberculosis has also been linked to impaired cellular immunity. Beck et al. demonstrated a highly significant difference in CD4 and CD8 cell counts between active TB patients compared with healthy controls [8]. A similar study by Al-Aska et al. not only supported this association, but revealed post treatment CD4 and CD8 counts which trended towards normal [9]. This study also noted more profound lymphopenia in those with disseminated TB, defined by localization in more than one tissue (CD4 247 + 187) [9]. Therefore, our patient's CD4 count may have been lower prior to presentation. Yet, the mechanism of TB induced lymphopenia is poorly understood. One possible mechanism includes sequestration of T lymphocytes in highly infected tissues [9,10]. An alternative explanation is activation induced apoptosis. Coleman et al. examined the effects of TB infected alveolar macrophages on T cell variability in vitro. Infected macrophages caused a dose dependent, caspase dependent T cell apoptosis [10]. Interestingly, mycobacterial antigens promote the expression of inhibitory cytokines (Transforming growth factor beta (TGF-β), IL 10 and IL 35). This phenomenon results in the suppression of CD4 cell responses and contributes to immunosuppression. Thus, mycobacterial antigens increase susceptibility to other pathogens which require cell-mediated immunity for infection control [8,9,11] Nevertheless, further studies are needed to characterize the clinical importance of TB associated lymphopenia.

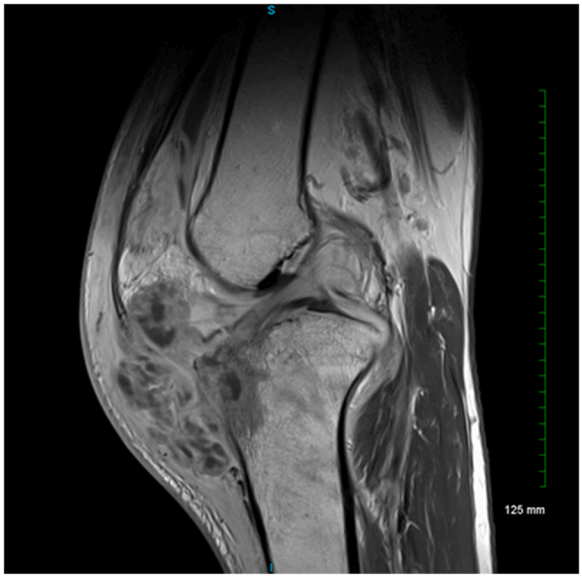

Fig. 1. Left Knee MRI: Joint effusion illustrating a 6 × 4 × 5 cm inflammatory mass identified within Hoffa's fat pad. Moderate to severe cartilage loss also observed with necrotic bone in the tibial plateau.

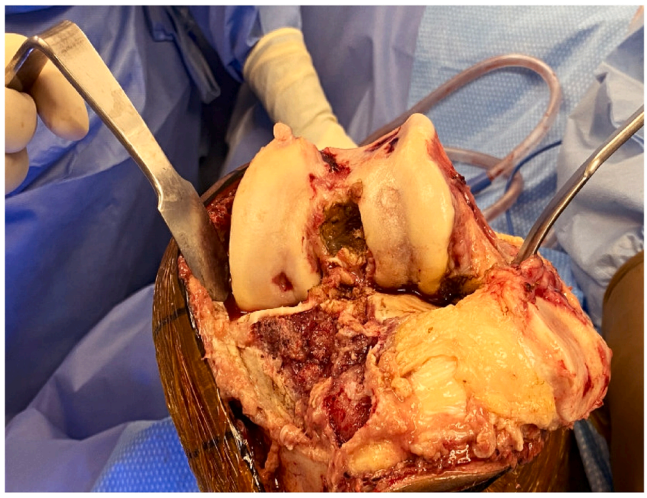

Fig. 2. Intraoperative picture of his left knee: Fistula noted on the medial aspect of the patellar tendon communicating with the anterior medial tibial plateau rim. Granuloma tissue can also be seen infiltrating the prepatellar bursa.

Co-infection with cryptococcosis and tuberculosis is a rare but important phenomenon. This co-infection has been previously observed in an immunocompromised patient with systemic lupus erythematosus [12]. Our case demonstrates that immunocompetent hosts are also at risk for cryptococcal and tuberculosis co-infection. The diagnosis of co-infection was made considering the TB effect on CD4 count resulting in cell mediated immunodeficiency. Although he was not evaluated for primary immunodeficiencies including gamma interferon deficiency or chronic granulomatous disease, he was diagnosed with active TB just seven months prior. Additionally, this case illustrates the importance of testing for occult infection in patients who do not improve despite appropriate treatment for their definite infection.

Sources of funding

No funding was required for this case report.

Ethical approval

N/A, as this is a case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Maxwell Isaac: Writing – original draft. **Paragkumar Patel:** Writing – review & editing. **Christian Rojas-Moreno:** Writing – review & editing, Supervision. **Thai Nguyen:** Writing – original draft. **Ramia Ahmed:** Writing – original draft.

Declarations of Interest

None.

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