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CASE REPORT PEER REVIEWED | OPEN ACCESS

Diagnosis of *Cryptococcus neoformans* in a soft tissue mass by fine needle aspiration in an immunocompetent patient

Negin Farsi, Rusella Mirza, Neesha Siriwardane, Ashley Flowers

ABSTRACT

Introduction: *Cryptococcus neoformans* is an encapsulated fungus present in the environment that primarily affects immunocompromised patients. Disseminated cryptococcosis is usually seen in immunocompromised patients and rarely in immunocompetent patients. It commonly involves the lung and central nervous system. Skeletal cryptococcosis is very rare. We present an interesting case of disseminated cryptococcosis with multiple lytic lesions of bone and a soft tissue mass in an immunocompetent patient. This type of clinical presentation in an immunocompetent person is extremely rare based on the English literature review.

Case Report: Our patient presented with worsening left knee pain over the past four months and swelling of the popliteal fossa of the left knee. He also complained of unintentional weight loss of 20–30 lbs, loss of appetite, night sweats, subjective fever, and chills. A computed tomography (CT) scan revealed an aggressive appearing soft tissue mass in the popliteal area infiltrating into adjacent bone, a lytic lesion in iliac crest, and one small lung nodule. Fine needle aspiration of knee mass revealed numerous fungal yeast forms. Morphology and ancillary tests were diagnostic of *C. neoformans*. Further workup revealed disseminated cryptococcosis despite of negative workup for immunodeficiency. The patient was treated with antifungal therapy and responded well.

Conclusion: Our article describes a rare presentation of disseminated cryptococcal infection and emphasizes the importance of considering cryptococcal infection as one of the differential diagnosis in any bone or soft tissue mass even in an immunocompetent patient.

Keywords: *Cryptococcus*, Fine needle aspiration, Immunocompetent, Knee pain

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INTRODUCTION

Cryptococcosis is caused by two agents namely *Cryptococcus neoformans* and *Cryptococcus gattii* [1]. Most disseminated cryptococcus infections are caused by *C. neoformans*, with world-wide distribution and mostly involving immunocompromised patients [2]. The most common predisposing factors to disseminated cryptococcal infection are HIV [1], chronic leukemia and lymphoma, long-term biological immunosuppressive therapy or corticosteroid, and diabetes and cirrhosis [3]. The *C. neoformans* pathogen, which is mostly found in soil and avian droppings [4], initially involves the lungs and then spreads hematogenously to the other organs [5]. Meningitis and meningoencephalitis are the most common presentation in disseminated cryptococcal infection, but it can also involve other parts of the body presenting as cutaneous infection, hepatitis, septic arteritis, and osteomyelitis [6]. Despite several case reports of disseminated cryptococcosis involving different areas of the body or organ systems in immunocompetent patients, there are only few cases being reported as

disseminated cryptococcal infection that presented initially with a focal soft tissue mass [6].

CASE REPORT

A 52-year-old African American man presented with worsening left knee pain over the past four months and swelling of the posterior part of the affected knee. He also complained of unintentional weight loss of 20–30 lbs, loss of appetite, night sweats, subjective fever, and chills. The patient was a truck driver and had no significant past medical history. Physical exam revealed swelling of the left knee with a soft tissue mass located at the popliteal region. The joint was tender and warm to touch. Magnetic resonance imaging demonstrated an aggressive appearing lesion measuring 4.3 × 4.6 × 3.9 cm with infiltration into bone at the proximal tibial metaphysis extending to the epiphysis, suggestive of a primary bone or soft tissue malignancy. Chest CT scan revealed a non-calcified solid nodule at the periphery of left lower lobe of the lung measuring 1.3 × 0.3 cm. The nodule was well-circumscribed with a focal spiculated margin. Another lytic lesion was identified in iliac crest. The differential diagnosis based on imaging characteristics included metastasis, myeloma, or lymphoma. The patient underwent ultrasound-guided fine needle aspiration and core needle biopsy of the left popliteal mass. Cytologic interpretation of the aspirate smears with Romanowsky stain was negative for malignant cells but revealed histiocytes, giant cells, and clusters of bland-appearing round structures of variable sizes with an abundant myxoid-like substance in the background. A transparent halo or capsule was present around those round structures (Figure 1A). Core biopsy revealed similar histological finding (Figure 1B). Periodic Acid-Schiff (PAS), Grocott's methenamine silver (GMS), and mucicarmine stains were performed on core biopsy. *Cryptococcus neoformans* were visualized as black round structures of variable sizes in GMS stain (Figure 1C). The mucoid capsule which is characteristic of *C. neoformans* stained dark pink with mucicarmine stain (Figure 1D). The morphology together with the characteristic staining pattern was diagnostic of *C. neoformans*. Subsequently, fine needle aspiration of the lung nodule showed benign lung parenchyma with mild chronic interstitial inflammation (Figure 2A) and no fungal component was identified on PAS (Figure 2B) and GMS stain (not shown). Subsequent laboratory workup was positive for cryptococcal antigen in serum and the cerebral spinal fluid (CSF), suggesting disseminated cryptococcal infection. Further workup for immunodeficiency including routine lab tests such as complete blood count, complete metabolic panel, and HIV Ag and antibody testing was negative. Also, the patient was healthy before this presentation and did not have any history of taking immunosuppressive medication.

The patient received intravenous Amphotericin B 3 mg/kg/day with flucytosine for two weeks with improvement of his symptoms. He was discharged upon completion of medical management and negative cryptococcal antigen in the CSF and was instructed to continue oral fluconazole 800 mg daily for eight weeks.

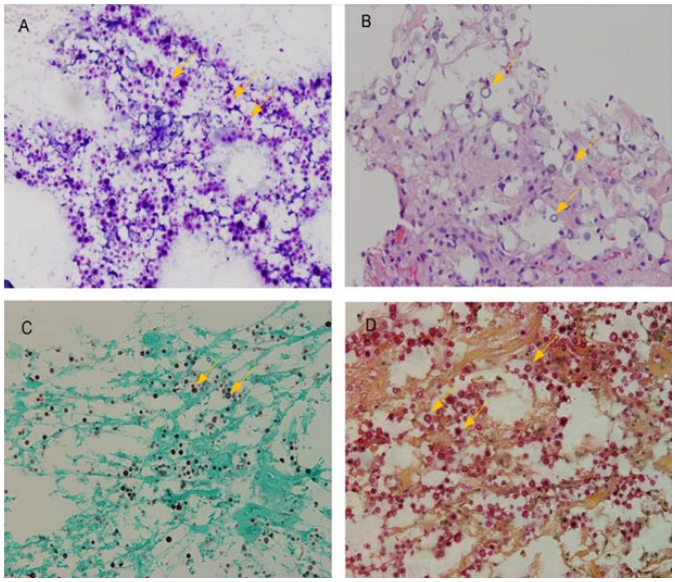

Figure 1: (A) Cytology demonstrates *Cryptococcus neoformans* as multiple round purple structures with pale white capsule around it. (B) Biopsy shows abundant foamy histiocytes and multiple round fungal yeast (arrows). (C and D) The fungal yeasts are positively stained with Grocott's methenamine silver and mucicarmine, respectively.

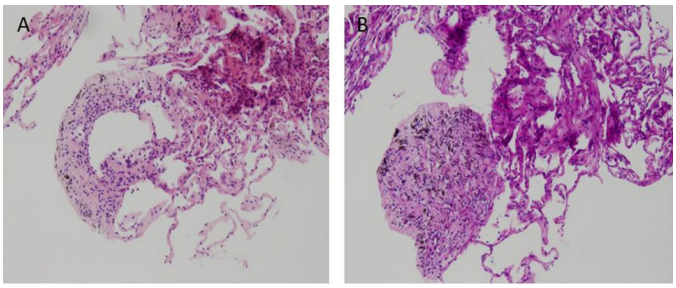

Figure 2: (A) Lung nodule biopsy demonstrating benign lung parenchyma with mild chronic interstitial inflammation and anthracotic pigments. (B) Periodic Acid-Schiff stain in lung nodule biopsy was negative for fungal elements.

DISCUSSION

We described a lytic bone lesion and aggressive soft tissue mass as a part of disseminated cryptococcal infection in an immunocompetent patient. Disseminated cryptococcal infection was previously defined as at least two positive cultures from two different sites [7]. Definition of invasive fungal infection has been revised in 2008 by Pauw et al. According to the consensus between European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG)

invasive fungal infection is defined as detection of fungus either by histological analysis or culture of the specimen tissue taken form the disease site. For cryptococcus to be considered as disseminated infection, positive capsular antigen in CSF would suffice irrespective of host factors or clinical features [8]. Very rarely, disseminated cryptococcus infection might be identified in immunocompetent patients [9]. The number of healthy patients with disseminated cryptococcal infection has increased since 2004 with an estimation of increase by 0.2 per million every year [10]. There have been case reports describing cryptococcal infection involving different organs or parts of body at the same time in healthy patients without any source of immunodeficiency. Most of these reported cases have primary pulmonary and cutaneous infections [11]. A much smaller number of case reports describe immunocompetent patients presenting with soft tissue infection, but all of them also had concomitant pulmonary and central nervous system (CNS) involvement [12]. A systematic review of all published cases of skeletal cryptococcosis between April 1977 and 2013 revealed patients who present with disseminated disease, regardless of their immune system status, can have unfavorable prognosis [13]. Our case presented with infiltrative and lytic lesion in the popliteal area and iliac bone and responded well with antifungal treatment.

Our case had classic features of *Cryptococcus* on fine needle aspiration of the popliteal mass. Also, cryptococcal antigen in serum and CSF were positive, tested with cryptococcal antigen latex agglutination system (CALAS) from Meridian which has 100% sensitivity and specificity [14].

Biopsy of the lung lesion only showed chronic interstitial inflammation and did not reveal any fungal elements. *Cryptococcus neoformans* pathogen, which is mostly found in soil and avian droppings [4], initially involves the lungs and then spread hematogenously to the other organs [5]. We believe that the nodular lung lesion was the probable site of the primary infection. The nodule size did not change with the treatment and repeated biopsy revealed similar findings. Our patient reported that he previously had bird droppings exposure at home as well as working as a trash collector for last 15 years in an urban environment which may expose him to cryptococcus infection.

CONCLUSION

Multiple lytic bone lesions, infiltrative soft tissue mass, and lung nodule are clinically suspicious for malignancy. Our case emphasizes on the importance of considering cryptococcal infection as one of our differential diagnoses in any bone or soft tissue mass. Early diagnosis and treatment in these patients can have greater impact on their outcome.

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Author Contributions

Negin Farsi – Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting

the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Rusella Mirza – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Neesha Siriwardane – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ashley Flowers – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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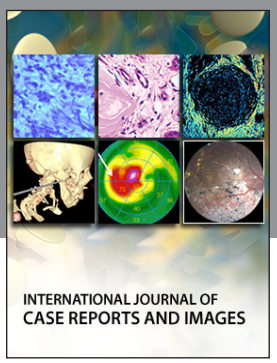

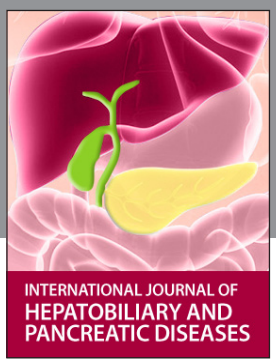

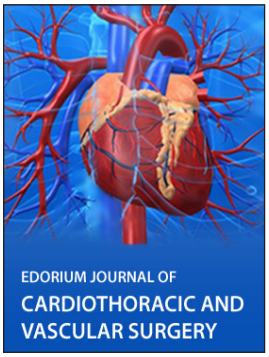

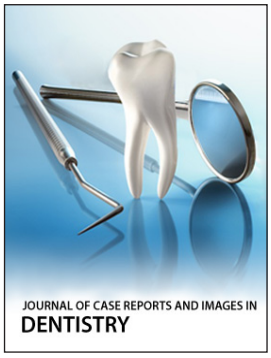

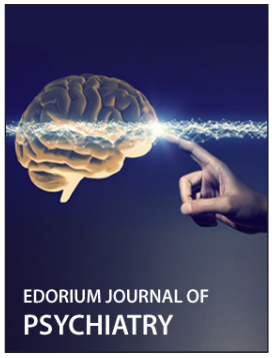

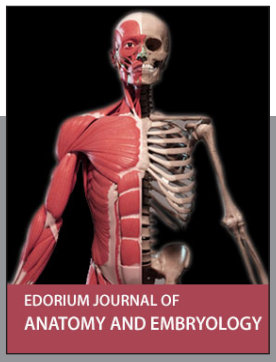

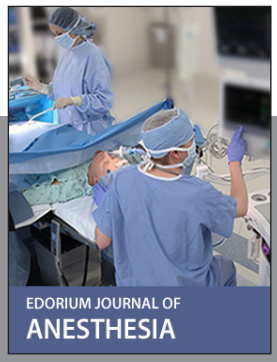

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