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Cryptococcal Osteomyelitis in an Adolescent Survivor of T-cell Acute Lymphoblastic Leukemia

Djin-Ye Oh, MD, PhD^{1,6}, P. Pallavi Madhusoodhan, MD, DCH², Deborah J. Springer, PhD³, Kenneth Inglima, MS⁴, Ali A. Chaudhri, MD⁴, Joseph Heitman, MD, PhD³, Elizabeth A. Raetz, MD^{2,5}, Alka Khaitan, MD¹, and Mona Rigaud, MD, MPH^{1,*}

¹Saul Krugmann Division of Pediatric Infectious Diseases, New York University Medical School

²Division of Pediatric Hematology and Oncology, Department of Pediatrics, New York University Medical School

³Departments of Molecular Genetics and Microbiology (MGM), Pharmacology and Cancer Biology, and Medicine, Duke University Medical Center

⁴Department of Pathology, New York University Medical School

⁵Division of Pediatric Hematology and Oncology, Department of Pediatrics, University of Utah School of Medicine

⁶Division of Infectious Diseases, Boston Children's Hospital, Harvard Medical School

Abstract

Cryptococcosis is infrequent in children and isolated cryptococcal osteomyelitis is rarely encountered. Here we describe a 14-year old patient in remission from T-cell acute lymphoblastic leukemia with osteomyelitis due to *Cryptococcus neoformans* var. *grubii*. The patient was effectively treated with antifungal therapy.

Keywords

Cryptococcus neoformans; Osteomyelitis; Leukemia

Introduction

Cryptococcus neoformans is a ubiquitous, encapsulated fungus recognized as a pathogen, with common reservoirs in pigeon guano and soil. Initial acquisition via the respiratory tract can result in clearance (most common), development of latency, or acute infection with possible dissemination. The clinical outcome correlates with host immune status. Symptomatic cryptococcosis represents either reactivation of latent infection, or primary infection^[1], and it typically occurs in immunocompromised individuals, affecting mostly the respiratory tract or the central nervous system. Other common sites of infection include skin,

*Corresponding Author: Mona Rigaud MD, MPH, Associate Professor, Saul Krugmann Division of Pediatric Infectious Diseases Department of Pediatrics, New York University Medical School, 550, First Avenue, New York, NY 10016, mona.rigaud@nyumc.org, Phone: 212-263-6426 | Fax: 212-263-7806.

eyes and prostate^[1]. Isolated cryptococcal osteomyelitis is rare, particularly in the pediatric population, in whom only 14 cases have been reported worldwide (Table 1)^[2-15]. Here we report a case of isolated osteomyelitis caused by *C. neoformans* in an adolescent survivor of T-cell acute lymphoblastic leukemia (T-ALL).

Case Report

A healthy 14-year old male, in remission from T-ALL, was admitted to the hospital after two days of progressive left ankle pain, not preceded by trauma. His past medical history was notable for T-ALL diagnosed 40 months prior to admission, for which he received over three years of systemic chemotherapy on the current Children's Oncology Group protocol for T-ALL. Complete remission was documented after four weeks of induction treatment and he received the final doses of maintenance therapy, which included intrathecal methotrexate, monthly pulses of prednisone and vincristine, daily 6-mercaptopurine and weekly methotrexate, one week prior to admission. The patient also had a history of asthma and steroid-induced diabetes. His medications consisted of prophylactic trimethoprim-sulfamethoxazole, insulin, fluticasone and albuterol. He lived in the Brooklyn borough of New York City; there was no recent history of close exposure to birds.

Physical examination revealed no significant abnormality except for left ankle swelling and tenderness. Laboratory tests were notable for neutropenia, lymphopenia and elevated inflammatory markers (Fig. 1A and Tables in Supplemental Digital Content (SDC) 1 and 2 summarizing laboratory findings). Left lower extremity radiograph showed a lytic defect in the anterior talus. Magnetic resonance imaging (MRI) revealed an intraosseous abscess and probable osteomyelitis of the talus (Fig. 1B). The patient underwent surgical irrigation and debridement of the bone, and empiric treatment with vancomycin was initiated. Bacterial cultures of three bone aspirates obtained during surgery yielded no pathogen (Fig. 1A). Postoperatively, the patient received granulocyte colony-stimulating factor twice for continued neutropenia. He improved and was discharged home on intravenous vancomycin, which was later transitioned to oral linezolid.

Following physical exertion two weeks later, painful ankle swelling recurred and he was readmitted. Physical examination showed a well-healing incision. Laboratory investigations revealed a rise in C-reactive protein and erythrocyte sedimentation rate, a normal white blood cell count, and normal galactomannan and (1-3)- β -D-glucan serum levels. Repeat MRI scan demonstrated persistent talar osteomyelitis with reaccumulation of the intraosseous abscess (Fig. 1C). A second talar curettage and irrigation was performed, followed by broad spectrum antibiotics. Copious purulent material from the intraosseous abscess was sent for bacterial and fungal cultures. His antibiotic regimen of linezolid and ciprofloxacin was changed to meropenem on the second postoperative day. Irrigation and debridement were repeated on the third postoperative day, followed by significant improvement of clinical and laboratory findings.

After eight days of incubation, a fluid aspirate, inoculated into enriched medium (Bact/Alert™ blood culture system, BioMérieux) during the second surgery, grew budding yeast, with fungal staining results suggestive of *Cryptococcus spp.* Further characterization (see

Table in SDC3 for a summary) confirmed the isolate¹ as *C. neoformans* var. *grubii*, prototrophic, molecular type VNI, mating type *MATa*, based on phenotypic characteristics, sequencing of the *ITS-Rlsu*², *MPD1*, *IGS1*, *TEF1* and *ATP6* regions, PCR analysis of the *MAT* gene *STE20*, and controlled mating assays with the *C. neoformans* var. *neoformans* strain JEC20a^[16] (Fig. 1E-G). Minimal inhibitory concentrations (MICs) indicated susceptibility to amphotericin B (MIC=1 µg/ml), fluconazole (2) and voriconazole (0.015), intermediate sensitivity to flucytosine (8), and caspofungin resistance (8). All other cultures remained negative (Fig. 1A). Histopathological study of the talar bone fragments gathered during the last two surgeries revealed several foci of acute and chronic inflammation and budding yeast forms (Fig. 1D).

Serum cryptococcal antigen (Ag) titer was 1:16; retrospective analysis of a serum specimen frozen at hospital admission, revealed a titer of 1:64. CSF studies were entirely within normal limits, including absence of cryptococcal Ag and negative fungal cultures. Blood cultures remained negative. Chest radiograph and chest computed tomography did not show any infiltrates. Ophthalmological evaluation revealed normal retinal and optic nerve. CD4/CD8 ratio was 1.121, with 135 CD4 cells/µl and 121 CD8 cells/µl.

Treatment with liposomal amphotericin B (4 mg/kg/day) and flucytosine (100 mg/kg/day) was administered for a total of two weeks, during which time he regained the ability to bear weight and inflammatory markers improved. He was discharged home on oral fluconazole (800 mg/day) for consolidation. Fluconazole was then tapered to 400 mg/day, which he is currently receiving on an ongoing basis. On follow up a year later, the patient continues to do well and his serum cryptococcal Ag is negative.

Discussion

In pediatric populations, subclinical infection with *C. neoformans* is common in certain geographic areas, with evidence for seroconversion occurring below the age of 10 for most children in New York City^[17,18]. Symptomatic cryptococcosis, in contrast, is unusual and its incidence is vastly lower than in adults^[19-23]. The basis for this age-related discrepancy of incidence remains unclear; potential contributing factors may be the shorter duration of infection, a lower cumulative exposure to *Cryptococcus spp.*, and differences in the epidemiology of the infecting strains^[24-26].

Symptomatic cryptococcosis can affect virtually any tissue or organ, but in the majority of cases it presents as neuromeningeal disease, with clinical signs of chronic meningitis and typical laboratory findings (positive CSF culture and antigen studies) and/or pneumonia. Extrapulmonary, nonmeningeal disease is considered the clinical entity studied the least, and it has been postulated that delays in diagnosis and institution of therapy due to atypical presentation may contribute to its overall poorer prognosis^[27]. It is usually the consequence of hematogenous seeding from a latent focus of infection and may present as acute disseminated (defined as involvement of at least 2 noncontiguous sites or evidence of high

¹W52233

²GenBank accession number KM085009

fungal burden based on cryptococcal antigen titer 1:512^[28]) or localized disease^[1]. Accurate data on the incidence of cryptococcal osteomyelitis is not available. Bone or joint involvement occurs in up to 5% of patients with disseminated disease, but isolated cryptococcal osteomyelitis is an atypical clinical manifestation^[29]. There is only one previous report of skeletal cryptococcosis in a child with ALL; this patient had disseminated, rather than isolated disease, presenting with pulmonary and CNS involvement in addition to osteomyelitis of the calvaria^[30].

To our knowledge, 14 cases of isolated cryptococcal osteomyelitis have been reported in children (Table 1)^[2-15]. The median age of these patients was 10 years (range, 1–18 years). Underlying risk factors, such as steroid therapy or primary immune deficiency were identified for four individuals. In the majority of cases, a single site was involved. All types of bones were affected, including long (9 cases), flat (3 cases), short (1 case), and irregular bones (3 cases). There are no distinct clinical features that typify cryptococcal osteomyelitis in children. This case, as in previous reports, is characterized by localized pain and swelling, mild constitutional symptoms and elevated inflammatory markers. The classic radiographic findings of lytic lesions with little or no periosteal reaction are equally nonspecific with a differential diagnosis including infection with *M. tuberculosis*, fungi, bacteria or malignancy. As in previous cases, definitive diagnosis was established by the demonstration of *C. neoformans* var. *grubii* in the affected bone by culture. It is noteworthy that the organism was recovered from only one of a total 10 intraoperative specimens obtained for culture, 38 days after the initial presentation. The positive specimen had been inoculated into blood culture bottles. Conventional fungal cultures, as well as five more samples cultured in blood culture medium remained negative. These findings potentially reflect low fungal burden, but do suggest that enriched liquid media and prolonged incubation times should be considered when cryptococcal osteomyelitis is suspected. Use of newer, antigen-based or molecular techniques may optimize timeliness of diagnosis and initiation of antifungal therapy^[31].

Our patient's isolate was classified as *C. neoformans* var. *grubii* (serotype A), genogroup VNI. Of the two *C. neoformans* varieties, *C. neoformans* var. *grubii* (serotype A) is distributed globally and causes the majority of clinical infections^[32], whereas *C. neoformans* var. *neoformans* is responsible for 5% of infections only and more prevalent in Europe than in North America. Genogroup VNI is the most prevalent of the three *C. neoformans* var. *grubii* genotypes circulating worldwide (VNI, VNII and VNB)^[33] and has been found in a large variety of clinical specimens. Although recent data indicates a prognostic impact of genotype at least in meningitis patients^[34], little is known on whether and how cryptococcal genotype affects the location and clinical course of infections other than meningitis. Genotyping results are relevant epidemiologically, but do currently not have implications for the clinical management of cryptococcosis^[35]. As expected, this isolate belonged to mating type *MATa*, reflecting the significant bias of mating type *MATa* over mating type *MATα* in clinical isolates from adults and children alike^[26]. Whether the greater virulence of this mating type observed in animal models^[36] is relevant clinically, is currently unclear^[37,38].

Due to the rare frequency of cryptococcal osteomyelitis, there is a lack of evidence-based treatment studies. Curettage combined with antifungals has been the most common approach

since the advent of amphotericin B^[29]. Our patient was severely immunocompromised at the time of diagnosis. Therefore, even though acute dissemination had been formally ruled out, our therapeutic strategy was broadly based on the revised IDSA guidelines^[28] for disseminated disease. For rapid reduction of fungal burden, curettage was followed by induction therapy with liposomal amphotericin B and flucytosine, which can be regarded as beneficial even in the absence of full flucytosine susceptibility^[39]. For maintenance therapy, a high dose of fluconazole was chosen, given that the infection affected a devascularized area in the setting of host immunocompromise^[28].

Underlying immunocompromise, specifically a deficiency of the cellular immunity, is the single most important risk factor for cryptococcosis. Our patient had just completed a protracted chemotherapy regimen that included corticosteroids and was profoundly lymphopenic prior to onset of the infection. For children as well as adults, major predisposing conditions include advanced HIV disease, high dose steroid therapy, malignancies, and solid organ / bone marrow transplantation^[1,20]. Non-HIV associated cryptococcosis in children is frequently associated with ALL^[40]. For 39 children hospitalized with nonmeningeal cryptococcosis, malignancy was observed in 12 (31%) cases, representing the most frequent comorbidity. The majority of these (at least 7) had lymphoblastic leukemia^[40].

This report of cryptococcal osteomyelitis in a patient with T-cell ALL supports the consideration of *C. neoformans* as a possible etiology of osteomyelitis in children with malignancies. Diagnostic workup in these patients should involve the use of enriched liquid media for cultures, specific fungal stains, measurement of cryptococcal Ag titers, and potentially the application of molecular diagnostic methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Laboratory and Imaging Studies over Time

Time course of laboratory findings and antimicrobial treatment (A); STIR- weighted MRI images of the left ankle at initial presentation (B) and on re-admission a month later (C), demonstrating size increase of an intraosseous abscess (→) within the head and neck of the talus and extensive surrounding marrow edema corresponding to osteomyelitis³; histopathological images (×40 magnification) showing cryptococci within the bone using GMS stain (D); robust mating between the clinical isolate (mating type α) and the test strain (mating type a), indicated by the presence of hyphae at the mating patch edge (×10, E), and basidia with chains of basidiospores (×40, F; ×100, G). Day 1 denotes the day of the first hospital admission, prior to which the patient was neutropenic and lymphopenic. WBC, White Blood Cell Count; ANC, Absolute Neutrophil Count; ALC, Absolute Lymphocyte

³Shown also is an irregularity to the distal tibia representing avascular necrosis, which is unrelated to the infectious process reported here.

Count; Cip., Ciprofloxacin; Merop., Meropenem; Flucon., Fluconazole; I&D, surgical irrigation and debridement.

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Table 1

Reported cases of isolated cryptococcal osteomyelitis in children

Patient no.	Reference	Patient Sex/Age [years]	Risk factor	Site involved	Diagnosis	Treatment	Outcome
1	Gosling and Gilmer, 1956 [2]	M / 10	none	radius, clavicle	culture, histopathology	Curettage	Asymptomatic at 20 months
2	Morris and Wolinsky, 1965 [3]	M / 17	none	L1 vertebra, 12th rib	culture	Curettage, AmB, Fluconazole	Asymptomatic at 4 weeks
3	Chleboun and Nade, 1977 [4]	M / 15	Tb ⁺	humerus	culture (in vitro and in animals)	Biopsy, AmB	Asymptomatic at 2 years
4	Poliner, et al., 1979 [5]	$\frac{4}{1} \frac{1}{12}$ M /	none	C2/C3 vertebrae	culture	Curettage, AmB, Flucytosine	Asymptomatic at 16 months
5	Fialk, et al., 1981 [6]	M / 9	none	tibia	histopathology	Biopsy, AmB	Asymptomatic at 2 years
6	Fialk, et al., 1981 [6]	M / 18	none	tibia	culture, histopathology, aspirate: Ag +ve	Curettage, AmB	Asymptomatic at 2 years radiograph: healing
7	Hammerschlag, et al., 1982 [7]	F / 11	none	femur	culture, histopathology	Curettage, AmB, Flucytosine	Asymptomatic at 4 months
8	Reinig, et al., 1984 [8]	F / 10	Lupus erythematosus Systemic steroid therapy	calvaria	culture	Curettage, AmB, Flucytosine	Deceased from pneumonia on post operative day 10
9	Zach and Penn, 1986 [9]	F / 13	none	femur	culture, histopathology	Curettage, AmB, Flucytosine	Asymptomatic at 24 months radiograph: healing
10	Baldwin, et al., 1988 [10]	F / 10	none	ilium	culture, histopathology	Biopsy, AmB, Flucytosine	Asymptomatic at 8 weeks
11	Govender, et al., 1988 [11]	F / 5	none	femur	culture	Curettage	Asymptomatic at 18 months radiograph: healing
12	Abdul-Karim, et al., 1991; Sorensen, et al., 1992 [12, 13]	M / 9	Interleukin-2 deficiency	scapula	culture, histopathology	Biopsy, AmB, Flucytosine	Asymptomatic at 4 years
13	Raftopoulos, et al., 1998 [14]	F / 14	none	rib	culture	Curettage, AmB, Fluconazole	Asymptomatic at 4 weeks
14	Jirapongsananuruk, et al., 2012 [15]	M / 3	IL12RB1 compound mutation	calcaneus	culture	Curettage, AmB, Fluconazole	Asymptomatic at 3 years

Patient no.	Reference	Patient Sex/Age [years]	Risk factor	Site involved	Diagnosis	Treatment	Outcome
15	This Report	M / 14	T-ALL in remission	talus	culture, histopathology	Curettage, AmB, Flucytosine; Fluconazole	Symptom improvement on antifungal therapy

Tb mediastinal abscess diagnosed during admission. Deceased two years later from Tb hepatitis and staphylococcal pneumonia.