

## Fusarium Osteomyelitis in a Patient With Pearson Syndrome: Case Report and Review of the Literature

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*Fusarium* species are ubiquitous fungi causing a wide array of infections, including invasive disease in the immunosuppressed. We present a fusarium bone infection in a child with Pearson syndrome and review the literature. Ten cases of fusarium osteomyelitis were reported in the past 40 years, and we review the treatments.

**Keywords.** fusarium; immunocompromised; osteomyelitis.

*Fusarium* species are fungi ubiquitous in nature and responsible for a wide array of infections in humans. Whereas keratitis and onychomycosis are the more common clinical manifestations in immunocompetent hosts, fusarium is also responsible for more invasive and disseminated diseases in the immunosuppressed [1]. Bone involvement, however, is an uncommon manifestation. We recently managed a fusarium bone infection in a child with Pearson syndrome (a syndrome including myelodysplasia and impaired immunity). A literature review using the search terms “Fusarium” AND “Osteomyelitis” in Pubmed and Ovid Medline found only 10 reported cases of fusarium osteomyelitis in the past 40 years. In this report, we provide details of our case and review the available literature describing the antifungal treatment of fusarium osteomyelitis. We find that, to date, antifungal therapy alone without wide surgical excision or amputation has never successfully cured fusarium osteomyelitis in immunosuppressed patients.

### CASE PRESENTATION

The patient was a 2.5-year-old male with a history of Pearson syndrome. Pearson syndrome is caused by a de novo single

large mutation in mitochondrial DNA resulting in varying degrees of marrow failure, pancytopenia, and pancreatic insufficiency. Our patient had been on daily filgrastim therapy (G-CSF) for 2 years before presentation. Two months before presentation a bone marrow aspirate revealed a modest number of blast cells. Testing of 20 cells showed that 19 had 45 chromosomes, including X and Y, but lacked chromosome 7 (monosomy 7). Two weeks before presentation, the patient scraped his left first (great) toe on his tricycle. He developed a small, erythematous, scabbed lesion the size of a pencil head on the medial aspect of the toe. He was treated with a course of oral clindamycin, but progressive swelling and erythema led to hospitalization and intravenous vancomycin. At presentation his absolute neutrophil count was 6895. He did not improve over the next 2 days, and cefepime was added. Magnetic resonance imaging (MRI) demonstrated osteomyelitis of the distal half of the left first metatarsal with concern for sepsis of the first metatarso-pharyngeal joint. Voriconazole and ambisome were added at this time, and Orthopedics was consulted. Orthopedics performed aspiration of the first metatarsal, which produced a small amount of serosanguinous fluid. The fluid culture grew *Fusarium* species (not further speciated) in the presence of suppurative arthritis consistent with proven invasive fungal disease [2]. The patient remained on voriconazole and ambisome because, although definitive therapy for fusarium infections is yet to be elucidated, current data support this combination as first line [3].

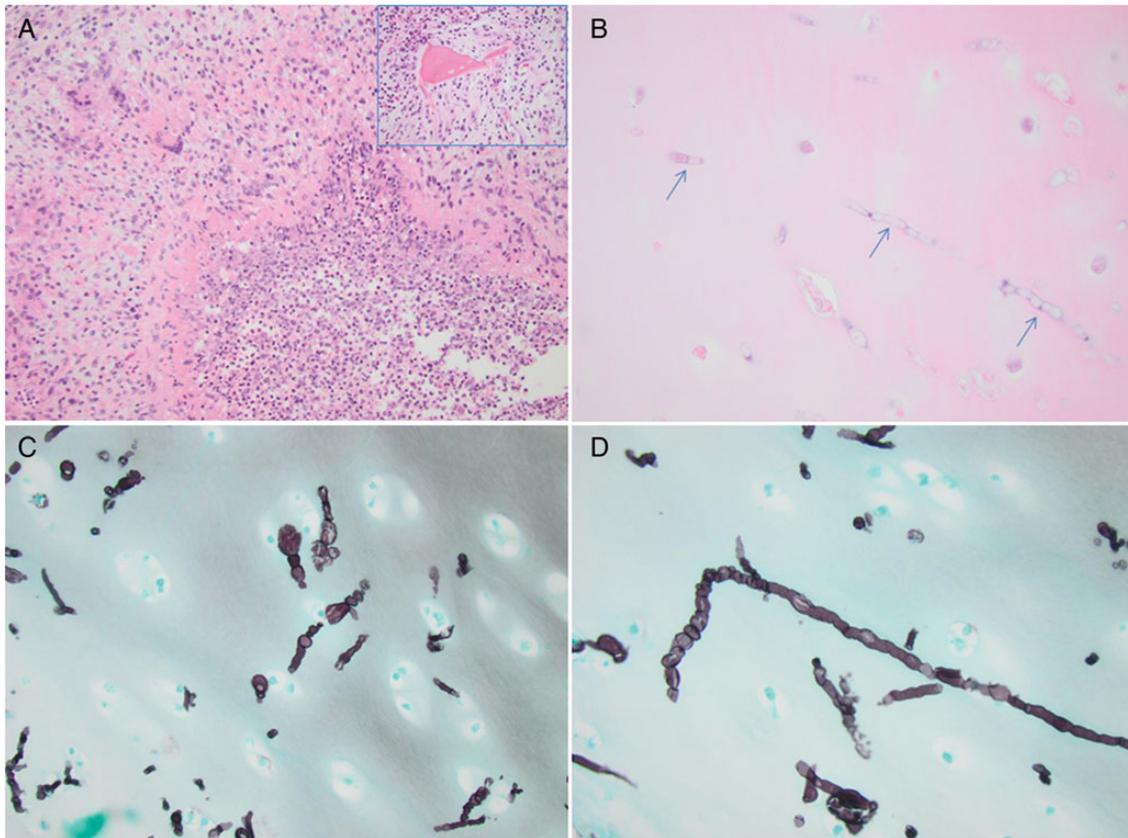
After 2 days of treatment, the toe appeared less erythematous. However, the patient developed severe hypotension, necessitating transfer to the pediatric intensive care unit and restoration of perfusion with intravenous fluids and dobutamine. Blood cultures (9 total) were negative for bacteria and fungi, and a computed tomography scan of the chest, abdomen, and pelvis showed no evidence of fungal dissemination. The patient was stabilized, but the edema and erythema of the foot did not improve, instead waxing and waning in intensity. A biopsy of the first metatarsal with washout of the joint was performed. The culture was negative for fusarium; however, the pathology report confirmed the presence of fungal elements with the appearance of fusarium in bone tissue fragments. The initial fusarium isolate was found to have a minimum inhibitory concentration (MIC) of 16 to voriconazole (and >16 for posaconazole and itraconazole), strongly suggesting resistance. The isolate was also found to have a MIC of 2 mcg/mL to amphotericin B. Therefore we discontinued voriconazole but continued amphotericin B in addition to caspofungin because of reported successful therapy of previously refractory fusarium infections using these drugs in combination [4]. The patient continued

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**Figure 1.** A, Histological sections of the tissue with focal abscess (right lower portion of the picture) with occasional multinucleated giant cells (left upper portion of the picture) and focal chronic inflammation with sequestered fragment of necrotic bone (inset), consistent with acute and chronic osteomyelitis (Hematoxylin and eosin,  $\times 200$ ). B, Histological section of the articular cartilage within the lesion containing multiple septated hyaline hyphae, some of which are indicated by arrows (H&E,  $\times 600$ ). C and D, Gomori methenamine silver stain reveals irregularly septate hyphae with focal acute angle branching ([C]: GMS,  $\times 400$ ; [D]: GMS,  $\times 600$ ).

on this regimen for 3 weeks with minimal clinical improvement. A repeat MRI demonstrated progression of bone destruction and joint space widening.

Due to the need for eradication of his osteomyelitis before a bone marrow transplant, as well as the concern for imminent transformation of his monosomy 7 into frank monocytic leukemia, he received a partial foot amputation just over 5 weeks after initial presentation. The orthopedic surgeons elected for partial amputation over wide surgical excision in this particular case because isolated removal of the joint would lead to foot instability and less functionality; the patient would have a better chance at future ambulation with the amputation. Although there was no visual evidence of osteomyelitis at the surgical margins, nevertheless Gomori methenamine silver and Periodic acid-Schiff stain were positive for fungal hyphae and yeast-like structures morphologically compatible with *Fusarium* species in the removed tissue (see Figure 1). This tissue also continued to demonstrate osteomyelitis with abscess formation around the base of the first toe involving the phalangeal-metatarsal bones. Therefore despite 5 weeks of antifungal therapy with 2 antifungal regimens, the proven invasive fungal disease had not been

eradicated. Following the amputation, caspofungin was discontinued 2 days after the amputation and amphotericin B was discontinued 7 days after the amputation. The patient subsequently underwent bone marrow transplantation successfully and had no evidence of recurrent infection in the lower extremity over the ensuing 7 months. After that time, however, the patient passed away after contracting a viral respiratory illness that progressed to respiratory failure and eventually renal failure as a result of his underlying metabolic disorder.

## DISCUSSION

The patient described herein was a 2.5-year-old male with Pearson's myelodysplasia, a syndrome associated with compromised resistance to infection [5]. He developed proven invasive fungal disease with fusarium infection from an innocuous injury and was initially treated with voriconazole and amphotericin. Clinicians often use voriconazole, amphotericin, or a combination of both to treat infections caused by this fungus, which can be difficult to eradicate. In 2014, the executive board of the European Fungal Infection Study Group (EFISG) and the European Confederation of Medical Mycology (ECMM) created pan-European

**Table 1. Summary of *Fusarium* Osteomyelitis Treatment and Outcomes 1976–2016**

	Clinical Presentation	Immune Status	Location	Treatment	Outcome	Author, Year of Publication
Case 1	7-y-old white male develops right tibial osteomyelitis 3 wk after falling and puncturing his right leg with a thorn.	Immunocompetent	Right tibia	Debridement + amphotericin B 5 mg IV daily for 15 d	Cured	Bourguignon et al 1976 [15]
Case 2	56-y-old female develops chronic osteomyelitis of the left fourth toe with a painful, nonhealing ulcer 1 y status after arthroplasty.	Immunocompetent	Left fourth toe	Digital amputation + topical antifungals	Cured	Page et al 1982 [18]
Case 3	34-y-old male develops leg osteomyelitis 2 mo after a motor vehicle accident with multiple injuries.	Immunocompetent	Lower extremity	Debridement + local amphotericin dressings	Cured	Nuovo et al 1988 [17]
Case 4	13-y-old male with relapsed acute lymphoblastic leukemia develops left triceps skin nodule with <i>Fusarium solani</i> and subsequently left tibial osteomyelitis.	Immunosuppressed: acutelymphocytic leukemia	Left tibia	Debridement + amphotericin B 1 mg/kg daily and rifampin 600 mg daily for 59 d (both discontinued due to renal failure)	Death (Sepsis with pulmonary disease thought to be disseminated fusariosis and eventually secondary AML)	Brint et al 1992 [12]
Case 5	52-y-old male with type 2 diabetes mellitus, end-stage renal disease, and congestive heart failure develops chronic osteomyelitis of the right foot with a painful, nonhealing ulcer for 4 mo.	Immunosuppressed: DM2	Right foot	Multiple left toe amputations with soft tissue growth of fungal elements resulting in left below knee amputation + voriconazole for 1 mo	Cured	Bader et al 2003 [9]
Case 6	14-y-old male with type 1 diabetes mellitus develops T12 vertebral osteomyelitis with both <i>Fusarium</i> and staph aureus.	Immunocompetent	T12 vertebral body	Amphotericin B 5 mg/kg IV daily for 4 wk + ketoconazole 5 mg/kg PO daily for 8 wk	Cured	Moschovi et al 2004 [16]
Case 7	65-y-old male with type 2 diabetes mellitus, chronic renal insufficiency, and pulmonary sarcoidosis treated with chronic low-dose steroids develops right fourth toe osteomyelitis.	Immunosuppressed: DM2 and chronic steroid therapy	Right first toe	Amputation of the right fourth toe + voriconazole 200 mg daily for 3 wk without improvement + eventual right below knee amputation	Cured	Sierra-Hoffman et al 2005 [11]
Case 8	92-y-old female with type 2 diabetes mellitus, chronic renal insufficiency develops chronic osteomyelitis of the right foot with a painful, nonhealing ulcer after several years of onychomycosis.	Immunosuppressed: DM2	Right foot	Debridement + itraconazole 400 mg/day (refusal of recommended amputation)	Death (bacterial superinfection, septic shock, and respiratory failure)	Wu et al 2009 [14]
Case 9	53-y-old female with an unnamed autoimmune disease on chronic steroid therapy develops chronic vertebral osteomyelitis and an epidural mass from a foreign body (bamboo splinter) lodged in the back during childhood.	Immunosuppressed: chronic steroid therapy	T12 vertebral body	Debridement with laminectomy x2 + amphotericin B 5 mg/kg IV daily for 13 wk and 6 mo of 400 mg oral posaconazole	Not cured; no longer a surgical patient now on long-term amphotericin B infusions	Edupuganti et al 2011 [13]
Case 10	School-age male with chronic granulomatous disease develops right ankle osteomyelitis after presenting with an erythematous, edematous ankle.	Immunosuppressed: chronic granulomatous disease	Right ankle	Wide surgical excision + amphotericin B 1 mg/kg IV daily and oral ketoconazole 150 mg daily for 6 wk	Cured	Bassiri-Jahromi et al 2012 [10]
Case 11	2-y-old male with Pearson syndrome develops chronic left toe osteomyelitis.	Immunosuppressed: Pearson syndrome	Left toe	Partial left foot amputation + amphotericin B and caspofungin for 3 wk	Cured	Hiebert et al 2016 (current report)

Abbreviations: AML, acute myelogenous leukemia; d, days; DM2, diabetes mellitus type 2; intravenous; IV, kg, kilograms; mo, months; mg, milligrams; PO, per os; T12, thoracic 12th vertebra; wk, weeks; y, year.

guidelines recommending a combination of voriconazole and a lipid formulation of amphotericin B as the optimal medical management for fusariosis based on the current data [3].

Unfortunately the patient responded poorly to combined therapy with voriconazole and amphotericin despite these being considered the most active drugs based on susceptibility profiles [6]. This was perhaps partially a result of the high MIC of the organism to voriconazole. Susceptibility testing and interpretation should be performed for fusarium infections because of this wide range of susceptibility profiles within the species, as well as for epidemiological reasons and to guide therapy in refractory cases. In this case, voriconazole had the best susceptibility profile compared with the other azoles. This has also been shown in in vitro studies comparing azoles, including isavuconazole, specifically in the treatment of fusarium [7]. These studies further suggest susceptibility breakpoints of 8 or 16 may be used for fusarium, but this is not an international standard. In view of this poor response, our next approach was treating him with amphotericin and caspofungin according to literature demonstrating successful eradication of refractory fusarium infections [4]. Furthermore, amphotericin and caspofungin have demonstrated in vitro synergy for clinical isolates of fusarium without the observation of antagonism [8]. After the original positive culture was obtained and therapy started, cultures of bone fragments of the affected bone did not grow fusarium. However, the pathologist reported the persistence in bone tissue of fungal elements consistent with the appearance of fusarium. The lack of any clinical response and the persistence of operative findings of osteomyelitis and joint abscess suggest the bone infection had not been eradicated.

We found 10 case reports of *Fusarium* species osteomyelitis written in the English language in the literature dating from 1972 to 2012 (see Table 1). Every case meets criteria for proven invasive fungal disease according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [2]. With the inclusion of the present case report, 7 of these infections occurred in immunosuppressed individuals. Of the immunosuppressed group, each of the 4 treated with wide surgical excision or amputation and antifungal therapy had the infection successfully eradicated [9–11]. Conversely, each of the 3 patients treated with simple debridement and antifungal therapy were not cured [12–14]. Ominously, 2 of these patients died during treatment, and the last appeared terminally ill at the time of the publication. The 4 cases of fusarium osteomyelitis occurring in immunocompetent patients were cured by combined surgical (either debridement or amputation) and antifungal therapy [15–18].

Given the lack of clinical trials and insufficient data, the optimal treatment strategy for fusarium infections remains unknown; outcomes, however, are heavily influenced by surgical control of infection and the net state of immunosuppression,

with immune reconstitution itself being paramount to patient survival. Although the present literature is limited by the low number of reports of fusarium osteomyelitis, of great interest is the fact that there are no cases demonstrating long-term definitive cure in an immunosuppressed individual with simple debridement and antifungal therapy alone. Review of the available cases would suggest that fusarium bone infections occurring in immunocompromised patients should be managed with wide surgical excision or amputation of the affected bone. Less aggressive therapy will likely fail, with a possibly increased risk for progression of disease and even death.

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