**Scedosporium prolificans** Osteomyelitis in an Immunocompetent Child Treated with a Novel Agent, Hexadecylphosphocholine (Miltefosine), in Combination with Terbinafine and Voriconazole: A Case Report

Alison M. Kesson,1,2 Michael C. Bellemore,2 Timothy J. O’Mara,2 David H. Ellis,3 and Tania C. Sorrell1,2

Departments of 1Infectious Diseases and Microbiology and 2Orthopaedics, The Children’s Hospital at Westmead, 3Centre for Infectious Disease and Microbiology, University of Sydney at Westmead, and 4Department of Infectious Diseases, Westmead Hospital, Westmead, 3Discipline of Paediatrics and Child Health, University of Sydney, Sydney, and 4Women’s and Children’s Hospital, North Adelaide, Australia

We describe an 8-year-old girl who sustained multiple compound fractures in an accident involving agricultural equipment. She developed *Scedosporium prolificans* osteomyelitis of the pelvis, septic arthritis of the hip, and myositis of adjacent muscles. The infection progressed, despite extensive surgical debridement and joint washouts with 0.2% polyhexamethylene biguanide; antifungal therapy with caspofungin, terbinafine, and voriconazole; and adjunctive therapy with interferon-γ. Gradual resolution was achieved after the addition of a novel agent, hexadecylphosphocholine (miltefosine), and the continuation of terbinafine and voriconazole. This is the first report of the use of miltefosine as an antifungal agent in the management of severe infection with *S. prolificans*.

**Case report.** A previously healthy 8-year-old immunocompetent girl fell into a rotary harvester on 3 October 2006, sustaining multiple injuries. These included an open fracture of the right iliac wing of the pelvis. Surgical specimens from her right iliac crest grew 2 strains of *Bacillus cereus*, *Klebsiella oxytoca*, *Enterobacter cloacae*, *Leclercia adecarboxylata*, viridans streptococcus, *Mycobacterium fortuitum*, and *Fusarium indicum*. She was treated with vancomycin, imipenem, ciprofloxacin, and voriconazole and was discharged from the hospital on 27 October, receiving ciprofloxacin. At discharge, her neutrophil count was $4.3 \times 10^9$ cells/L, and her C-reactive protein level was 40.5 mg/dL. Two weeks later, she returned with severe pain in her right hip, neutrophilia (neutrophil count, $13.2 \times 10^9$ cells/L), an erythrocyte sedimentation rate of 140 mm/h, and a C-reactive protein level of 134 mg/dL. MRI of the hip and pelvis showed dislocation of the right hip joint secondary to a septic effusion, evidence of osteomyelitis involving the acetabulum and right iliac wing with myositis involving the glutei and iliaceus, and enlarged right inguinal, internal iliac, and paravertebral lymph nodes (figure 1). She underwent arthroscopy, drainage of pus, and debridement. The hip was reduced and splinted in abduction, and she was given meropenem, ciprofloxacin, and, because of previous isolation of *Fusarium* species, liposomal amphotericin B (Ambisome). Culture of the pus grew *Scedosporium prolificans* that was resistant to amphotericin B (MIC, 16 mg/L), 5-flucytosine (MIC, $>64$ mg/L), fluconazole (MIC, $>256$ mg/L), itraconazole (MIC, $>16$ mg/L), ketoconazole (MIC, 16 mg/L), and voriconazole (MIC, 8 mg/L) and that was intermediately susceptible to terbinafine (MIC, 2 mg/L). Synergy was demonstrated with terbinafine and voriconazole (combined fractional inhibitory concentration, 0.266 µg/mL) but not with terbinafine and itraconazole (combined fractional inhibitory concentration, 0.141 µg/mL) [1]. On 6 December, amphotericin B, meropenem, and ciprofloxacin were ceased, and voriconazole was increased by 6 mg/kg every 12 h to 24 h and then to 4 mg/kg every 12 h as well as terbinafine at 125 mg daily were commenced. Six days later, MRI showed a large, recurrent right hip joint inflammatory phlegmon with new erosive changes involving the right acetabulum and femoral head. Marked inflammatory changes in the right iliopsoas and gluteal muscles were unchanged, but increased enhancement of adductor muscle groups bilaterally suggested progression of infection. Caspofungin at 500 mg/m² daily [2] and IFN-γ at $1 \times 10^8$ U/m² 3 times weekly were added.

There was considerable concern about the patient’s prognosis, particularly that her illness was life threatening without radical debridement (hindquarter amputation); however, this treatment option was possible only if a clear surgical margin could be achieved by demonstrating that the enlarged iliac and paravertebral lymph nodes were not infected. On 14 December, she underwent surgery to debulk the large amount of infected and dead tissue and to define a surgical margin. Reaccumulated...
Figure 1. T1-weighted coronal (A) and axial (B) images from pelvic MRI with gadolinium, from November 2006. The images show dislocation of the right hip joint, with the head of the femur displaced superolaterally by a moderate to large joint effusion. Within the joint effusion there are areas of reduced signal intensity, which may be due to pus or blood. Bone marrow edema is also seen within the head and proximal shaft of the right femur. There is bone marrow edema involving the roof of the right acetabulum and adjacent right iliac bone, with destruction of the cortex. The overlying subcutaneous tissues also demonstrate enhancement. Within the pelvis there is hyperintensity and enhancement of the right iliopsoas, obturator internus, piriformis, and obturator externus muscles. Enlarged lymph nodes are seen in the right inguinal, internal iliac, and paravertebral lymph nodes. There is no evidence of intrapelvic collection. Incidentally, the bladder is full.

Pus in the right hip was drained; infected necrotic bone, cartilage, and joint capsule were resected from the iliac wing and hip joint; and the hip joint was lavaged with 0.2% polyhexamethylene biguanide [2]. Several macroscopically involved muscles around the right hip were partly resected, including the iliacus, rectus femoris, gluteus medius, and sartorius. S. prolificans was cultured from the excised muscles, bone, and capsule but not from biopsy specimens from the psoas muscle or internal iliac lymph nodes, indicating that a surgical margin was attainable.

In view of the progressive disease, hexadecylphosphocholine (miltefosine; Zentaris), an oral antileishmanial drug that has in vitro antifungal activity against some yeasts and filamentous fungi (including S. prolificans) [4], was tested for activity against the patient’s isolate and gave a MIC and minimum fungicidal concentration of 2 mg/L. Miltefosine was added on 28 December at 2 mg/kg/day, the dose recommended for treatment of visceral leishmaniasis [5]. Repeat MRI on 2 January 2007 showed reaccumulation of fluid in the hip joint, which tracked superiorly along the iliac bone. On 4 January, pus that grew S. prolificans was again drained from the hip joint, and the wound was left open. Lavage of the hip joint with polyhexamethylene biguanide and packing of the open wound were performed 3 times weekly for 2 weeks. S. prolificans was last cultured from
the joint fluid 21 days after the addition of miltefosine. The patient was discharged home on 23 February with an open granulating wound, taking terbinafine at 125 mg and 250 mg on alternate days, voriconazole at 9 mg/kg 3 times daily (trough levels, 1–1.5 mg/L), and miltefosine at 2 mg/kg/day divided 3 times daily. Miltefosine-induced nausea was controlled by divided daily doses and the use of ondansetron.

Over the next 4 months, the extensive open right hip wound was managed by daily dressings and was healed by secondary intention. The erythrocyte sedimentation rate fell from 150 to 3 mm/h, the C-reactive protein level fell from 184 to 2 mg/L, and the patient improved while receiving antifungal therapy, showing no evidence of hematological, renal, or hepatic toxicity. Skin toxicity resulted from voriconazole, with erythema, fragility, and development of lentigines occurring on sun-exposed areas. Voriconazole was ceased in October after 12 months of therapy; skin fragility resolved within a week, and the number of lentigines decreased over the next 3 months. Miltefosine was ceased in November, and terbinafine was ceased in December.

Repeat MRI in December 2007 revealed preservation of the hip joint, irregular articular margins, and an abnormal signal in the right femoral head and adjacent acetabulum (figure 2). Administration of gadolinium enhanced the joint capsule, the adjacent acetabulum, and surrounding soft tissues.
As of December 2008, no recurrence of infection had occurred. She could walk unaided without pain but did have a limp. Movement in the right hip was >50% of the normal range, which is remarkable given that it was expected to fuse. She was unrestricted in her daily activities, which included competitive sports and gymnastics.

**Discussion.** Invasive infections caused by *S. prolificans* are increasing in frequency, are associated with substantial morbidity, and have mortality rates of 55%–70%, despite the use of antifungal therapy with or without surgical debridement [6–9]. Penetrating trauma and surgery are major risk factors for invasive localized *S. prolificans* infection in healthy hosts [10], and infections in immunocompromised individuals are often disseminated and are generally fatal [11].

The optimal antifungal therapy for invasive *S. prolificans* infection has not yet been determined. In vitro MICs of antifungal drugs against most isolates of *S. prolificans* are relatively high, and amphotericin B, nystatin, 5-flucytosine, fluconazole, itraconazole, posaconazole, and the echinocandins do not have appreciable activity (Australian Scedosporiosis Study, unpublished data) [10, 12, 13], although caspofungin MICs against a few isolates have been 4–8 μg/mL. Of the later-generation triazoles, voriconazole exhibits the best activity, with MICs of 0.125–8 mg/L (MIC_{50/90} of 4.0/4.0–8.0 in some studies [Australian Scedosporiosis Study, unpublished data]) [14] but MIC_{50/90} of 8/8 in another [15]). MICs of terbinafine were high (≥8 mg/L) in one series [16], but isolates have appeared susceptible in others (range, 2–32 mg/L; MIC_{50/90} of 16/16–32 [10], MICs of 1–32 mg/L [17], and MICs of 1–4 mg/L [Australian Scedosporiosis Study, unpublished data]). Synergy between terbinafine and voriconazole has been demonstrated in vitro [14, 18]. Our patient’s isolate had a voriconazole MIC of 8 mg/L and a terbinafine MIC of 2 mg/L, and synergy was demonstrated by a checkerboard method; however, therapy with voriconazole plus terbinafine in combination with surgical debridement failed to contain the infection, and caspofungin was added to provide possible benefit [2]. A 0.2% solution of polyhexamethylene biguanide, a synthetic biocide, was used as a presurgical antimicrobial solution [2] to irrigate the infected hip joint and was continued. Because of presumptive immunodeficiency resulting from her catabolic state, IFN-γ was added [3]. None of these measures contained the infection.

Two weeks later, miltefosine, a phosphocholine analogue that is orally bioavailable (although highly protein bound [96%]) and that is widely distributed in the body, was commenced. It penetrates into the liver, kidneys, and spleen well; however, its ability to penetrate bone is unknown [19]. The terminal halflife of miltefosine is long; steady-state serum levels are generally 7–10-fold higher than the MIC of this patient’s *S. prolificans* isolate. With miltefosine therapy, there was a gradual normalization of the levels of inflammatory markers in blood, results of surgical cultures became negative, and the sinus that was draining the affected hip joint closed spontaneously.

Miltefosine is an alkylphosphocholine drug; it was initially and unsuccessfully investigated for use in anticancer therapy and is now marketed for treatment of infections with *L. major* species and *Trypanosoma cruzi* [5]. Previous in vitro studies have demonstrated that miltefosine is fungicidal and has a MIC and minimum fungicidal concentration of 4 mg/L against *S. prolificans*, compared with a steady-state serum level of 24 mg/L at 2 mg/kg/day [19]. The molecular targets and mechanisms of its antifungal effects are as-yet unknown; however, miltefosine is structurally similar to the natural substrates of phospholipase B, which is a virulence determinant in *Candida albicans* and *Cryptococcus neoformans* infections [20, 21] and is produced by *S. prolificans* and other filamentous fungi (T.C.S., unpublished data). Miltefosine may exhibit its antifungal effect by interfering with cell-wall synthesis or cellmembrane biochemistry [4]. It has a number of significant toxicities—nausea, vomiting, biochemical hepatotoxicity, and skin rashes, including Stevens-Johnson syndrome—making its long-term use potentially problematic.

This is the first report of the use of miltefosine in the management of an invasive fungal infection. Although the use of multiple therapeutic agents makes it difficult to attribute the observed therapeutic response to miltefosine alone, disease progression was reversed only after its commencement, and multiple infected tissues became culture negative within 3 weeks. This agent may be considered for use in salvage therapy for invasive fungal infections, for which there are currently very few effective agents.

**Acknowledgments**

We acknowledge the work of the Departments of Microbiology, Pharmacy, and Radiology at The Children’s Hospital at Westmead in assisting with the management of this patient.

**Potential conflicts of interest.** D.H.E. is a member of the advisory boards of and has received research funding from Pfizer, Merck Sharp & Dohme, Schering-Plough, Gilead Sciences, and Novartis. T.C.S. is a member of the advisory board of Pfizer and has received untied research grants from the company. Zentaris has provided free radio-labeled miltefosine for an unrelated study. All other authors: no conflicts.

**References**


