CASE REPORT

Recurrent *Scedosporium apiospermum* mycetoma successfully treated by surgical excision and voriconazole

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ABSTRACT

*Scedosporium apiospermum* is an emerging opportunistic fungus that can cause localized infection in healthy hosts or severe disseminated disease in immunocompromised hosts. Most cases are reported in Western Europe, Australia, and North America. We report a 52-year-old immunocompetent Taiwanese woman who presented with a 6-year history of recurrent asymptomatic papulonodular lesions on her right foot after minor trauma. Deep fungal infection caused by *Scedosporium* sp. was diagnosed after a skin biopsy with fungal culture of the skin specimen. She underwent two surgical excisions, each followed by a 4-month course of oral itraconazole and intralesional injections of amphotericin B as well, but similar lesions recurred at the same location 1 year later. She had another surgical excision and the pathological findings showed mycetoma. The fungus was identified as *S. apiospermum* by PCR assay of fungal culture specimen using the internal transcriber spacers (ITS1, similarity 99.4%; ITS2, similarity 100%) and the D1–D2 (similarity 99.0%) regions of the ribosomal operon. After 4 months of oral voriconazole (400 mg/day), no recurrence was noted in the subsequent 2 years.

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Introduction

*Scedosporium apiospermum* is an emerging opportunistic pathogen that can cause either disseminated disease in immunocompromised hosts or localized infection in immunocompetent hosts through trauma or surgery.1 Localized infections mainly affect the skin and soft tissue with extension to tendons, ligaments, and even the bone. Disseminated diseases may result in septic arthritis, pneumonia, endocarditis, meningitis, brain abscess, sinusitis, and/or keratitis. *S. apiospermum* is characterized by its resistance to commonly used antifungal drugs, such as ketoconazole, itraconazole, and amphotericin B.2–4 Most cases of mycetomatous *S. apiospermum* infections have been reported in Western Europe, Australia, and North America.5 We report the first Taiwanese patient with recurrent mycetomatous *S. apiospermum* infection successfully treated by surgical excision and oral voriconazole.

Case report

A 52-year-old Taiwanese woman came to our department due to recurrent asymptomatic papulonodular lesions on her right foot for 6 years. Erythematous nodular lesions were first noted on her right dorsal foot in October 2005 after minor trauma. Deep fungal infection caused by *Scedosporium* species was diagnosed after a skin biopsy and fungal culture of the biopsy specimen. She underwent two surgical excisions in October 2005 and April 2008, each followed by a 4-month course of oral itraconazole (300 or 400 mg/day). In addition, she was advised to use local thermal therapy by applying warm packs (~50°C, 30 minutes/day) for 2 weeks after the second surgical excision. Intralional injections of amphotericin B at a concentration of 5 mg/mL (once every other...
week for 6 times, total 30 mg) were also given from June 2008 to August 2008. Magnetic resonance imaging of the right foot in October 2008 revealed edema of the soft tissues around the second, third, and fourth metatarsals, and flexor tendons secondary to the recent surgery, but there was no specific infiltration. Unfortunately, similar lesions recurred at the same location in November 2009 (Figure 1A). She received another surgical excision in January 2010 (Figure 1B). Interconnected, twisted tubule-like fibroconnective tissue and yellow-brownish nodules within necrotic tissue were found during the operation (Figure 1C). Pathologic examination of the excised tissue showed features of mycetoma characterized by discrete nodular aggregates of fungal hyphae in multiple large abscesses in the reticular dermis surrounded by lymphocytes, histiocytes, and neutrophils (Figure 2A and B). The hyphae were further highlighted by periodic acid–Schiff (PAS) (Figure 2C) and Gomori methenamine silver (GMS) stains (Figure 2D). Fungal culture of the excised skin tissue yielded grayish white cotton-like colonies (Figure 3A). Microscopic examination revealed septate and branched hyphae with ovoid conidia born terminally on branched conidiophores or laterally on hyphae (Figure 3B). The fungus was identified to the species level S. apiospermum by PCR assay of the fungus from the culture using the internal transcriber spacers (ITS1, similarity 99.4%; ITS2, similarity 100%) and the D1–D2 (similarity 99.0%) regions of the ribosomal operon (Table 1). Treatment with oral voriconazole (400 mg/day) was initiated. Elevated liver enzymes (glutamic oxaloacetic transaminase (GOT)/glutamic pyruvic transaminase (GPT) = 176/131 U/L), however, were noted after 3 months, so voriconazole was held off for 1 week, and then was resumed when liver function tests returned to baseline level (GOT/GPT = 45/44 U/L). After a 4-month course of voriconazole, there was no recurrence in the subsequent 2 years (Figure 4).

**Discussion**

Serious infections caused by S. apiospermum have been increasingly reported in recent years. The sexual phase of S. apiospermum is *Pseudallescheria apiosperma*. Its occurrence is promoted in manure-enriched or polluted environments, such as agricultural land, garden soil, sewer or ditch mud, and polluted pond bottoms. Serious infection is more common in temperate climates and less frequently encountered in the tropics. S. apiospermum causes a wide spectrum of conditions, including mycetoma, colonization of the airways, sinopulmonary infections, extrapulmonary localized infections, and disseminated infections. The term “mycetoma” represents a chronic, progressive, indolent mycosis characterized by tumefaction (subcutaneous tissues become edematous), multiple draining sinuses, and extrusion of grains. Mycetoma can be caused by soil-inhabiting bacteria (actinomycosis) or fungi (eumycetoma). In one retrospective study of 63 cases in the United States, S. apiospermum is the most common fungal etiologic agent of mycetoma.

Histopathologically, mycetoma shows nodular aggregates of fungal hyphae, which are more easily demonstrated by PAS or GMS stains. In tissue sections, S. apiospermum displays septate and branched hyphae, and can be mistaken as *Aspergillus*, *Fusarium*, or other species of black fungi. Kimura et al found that the combination of haphazardly branching hyphae and lemon-shaped conidia was the most useful feature to differentiate *S. apiospermum* from other filamentous fungi in tissue.

Diagnosis of *S. apiospermum* infection is confirmed by culture of the infected tissue. The colony typically looks light to brownish gray with a mouse fur-like appearance in 1–2 weeks, but other morphologically similar species can make the identification of *S. apiospermum* difficult. In the present study, we applied PCR to amplify the ITS1, ITS2, and D1–D2 regions of 26S rDNA. The
amplicons were sequenced and the resulting sequences were used for searching homologous sequences in public databases using the BLASTN algorithm (http://www.ncbi.nlm.nih.gov/BLAST/). The BLAST search hit best-scoring sequences from *S. apiospermum* with 99.4% (ITS1), 100% (ITS2), and 99.0% (D1--D2) similarities.

Treatments of mycetomatous *S. apiospermum* infection include surgical debridement and antifungal therapy.14,15 The former should be applied if the lesion is localized.14 Antifungal therapy is considered as a conservative treatment for those who are too weak to have surgery or as an adjuvant treatment to surgery for refractory mycetoma. *S. apiospermum* has very high levels of resistance to conventional antifungal drugs.16 Among azoles tested for in vitro activity against *S. apiospermum*, voriconazole has the most potent effect (MIC50, 0.25 μg/mL), followed by miconazole (MIC50, 0.5 μg/mL), and albiconazole (MIC50, 0.5–1 μg/mL).12,17 On the contrary, itraconazole (MIC50, 4.5 μg/mL), ketoconazole (MIC50, 10.07 μg/mL), and amphotericin B (MIC50, 4 μg/mL) showed poor antifungal activity.12,17 Voriconazole is a broad-spectrum azole antifungal agent and can be administered intravenously and orally with excellent bioavailability.18 In a large series of 107 patients with scedosporiosis treated with voriconazole (6 mg/kg of body weight intravenously twice daily on Day 1, followed by 4 mg/kg intravenously twice daily...
and then switching to oral therapy at 200 mg twice daily), a successful therapeutic response was achieved in 57% of patients (median, 103 therapy days), with >98% of patients responding after receiving >28 days of therapy. The best therapeutic responses were seen for skin/subcutaneous (91%) or bone (79%) infections, and the lowest for central nervous system infections (43%).

Thereafter, sporadic cases with cutaneous *S. apiospermum* infections successfully treated by oral or intralesional voriconazole have also been reported. Although voriconazole is active against a broad range of fungal pathogens, several adverse events have been described, including reversible visual disturbances, hallucinations, abdominal pain, and hepatitis, allergic skin reactions, and, less frequently, lymphadenopathy or pan-cytopenia. Our patient had a transient elevation of liver function tests after 3 months of voriconazole administration, which recovered after the use of voriconazole was held for 1 week.

In summary, we report the first Taiwanese patient with recurrent mycetomatous *S. apiospermum* infection. The infection of the foot recurred twice after two surgical excisions plus oral itraconazole therapy, and was finally controlled by another surgical excision which was followed by a 4-month course of oral voriconazole.

References