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Scedosporium apiospermum infections and the role of combination antifungal therapy and GM-CSF: A case report and review of the literature

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ABSTRACT

Scedosporium apiospermum, a ubiquitous environmental mold, is increasingly reported as causing invasive fungal disease in immunocompromised hosts. It poses a therapeutic challenge due to its intrinsic resistance to traditional *anti*fungals and ability to recur despite demonstrating susceptibility. We present an immunocompromised patient with a cutaneous *S. apiospermum* infection that disseminated despite treatment with voriconazole, the drug of choice. Adding echinocandins and GM-CSF provided partial recovery, indicating a potential synergistic role of dual-antifungal and immunotherapeutic agents.

1. Introduction

Scedosporium apiospermum, once considered the asexual form of *Pseudoallescheria boydii*, is a filamentous fungus found worldwide in soil, sewage, and polluted waters [1]. Previously considered exceedingly rare, *S. apiospermum* is increasingly reported as a cause of opportunistic infection, as use of corticosteroids, immunosuppressants, antineoplastics, and broad-spectrum antibiotics have become more widespread [2]. Furthermore, it is thought that increased use of antifungals in immunocompromised patients with agents that have activity against *Candida spp.* and *Aspergillus fumigatus* but only modest or no activity against *Scedosporium* (*e.g.* amphotericin B and echinocandins), may exert a selective pressure and contribute to the increased incidence of *Scedosporium* infections [3].

S. apiospermum infections most commonly occur in the paranasal sinuses, lungs, skin, soft tissue, central nervous system, and bones, but disseminated disease is also common and often fatal [1]. Herein we report a case of disseminated infection from a cutaneous source in a patient exposed to steroids in which progression of disease was observed despite adequate treatment with voriconazole, the current drug of choice. *S. apiospermum* poses a therapeutic challenge due to its intrinsic resistance to commonly used antifungal agents and its ability to recur even when susceptibility to these medications is demonstrated. In our case, the addition of echinocandins and granulocyte macrophage colony-stimulating factor (GM-CSF) to the patient's treatment regimen provided partial recovery. This case demonstrates a potential synergistic role for dual-antifungal treatment with adjunctive immunotherapeutic agents in the treatment of *S. apiospermum* infections. As *S. apiospsermum* infections become increasingly prevalent, further consideration and investigation of this combination therapy is necessary to combat this highly fatal and aggressive organism.

2. Case

A 77-year-old man on high dose steroids for presumed temporal arteritis presented on day 0 with a 10 day history of progressive swelling, erythema, and pain of the left leg. He denied fever, chills, nausea, vomiting or diarrhea and denied any history of trauma or travel inside or outside the United States. The patient's past medical history included hypercholesterolemia, hypertension, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, benign prostatic hypertrophy and sphenoid sinusitis. He was admitted to the hospital on day 0 for treatment of leg cellulitis. Physical exam revealed diffuse, circumferential, macular erythema and warmth extending from the left ankle to the popliteal fossa. There were three, 5 mm pink papules with fine scale at the superior-most aspect of the erythema. On the anterior tibia there were two 1 cm flaccid bullae. The leg was non-tender. The patient received vancomycin and cefepime and after 7 days of therapy there was partial improvement of the erythema; however, on day +7, new diffuse, non-tender, 0.5–1.5 cm subcutaneous nodules emerged

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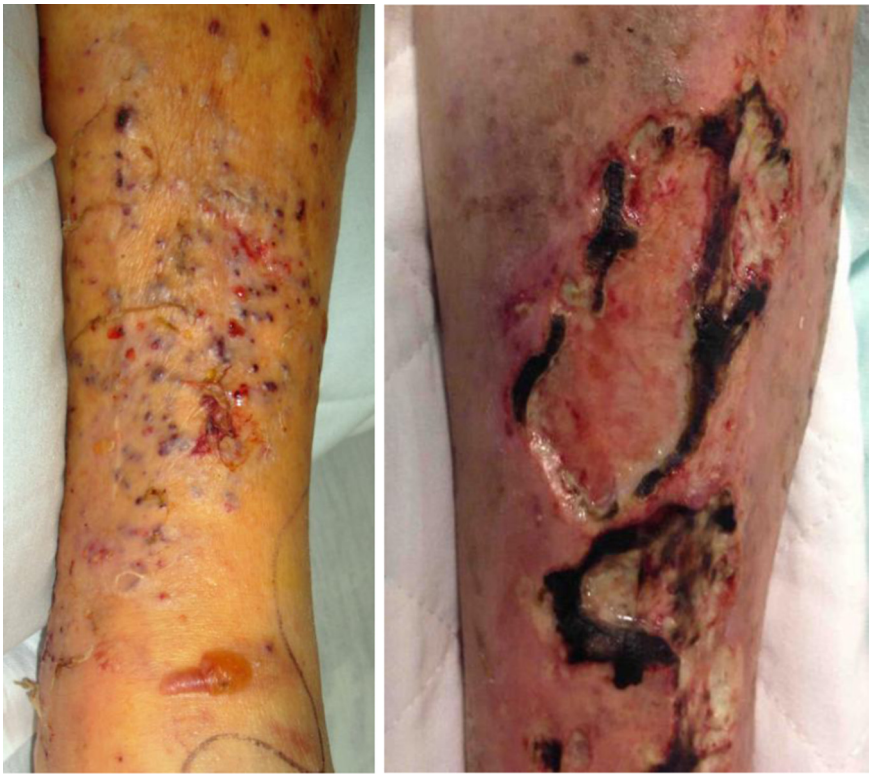

Fig. 1. A. Left shin on initial presentation after treatment with antibiotic therapy. B. Left shin lesion after addition of micafungin and GM-CSF. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

Table 1
Sensitivities of *Scedosporium apiospermum* isolate.

Antifungal	First admission MIC[a] (μg/ml)	Second admissions MIC[b] (μg/ml)	Synergy[b]	MIC[b] (μg/ml)	Interpretation
AMB	2	>2	AMB+CAS	>2+>4	Indifferent
MON	–	0.5	AMB+MICA	>2+>4	Indifferent
ITC	>16	–			
VRC	0.12	1	AMB+POS	2+4	Indifferent
POS	0.5	>4	AMB+VRC	2+0.5	Indifferent
MICA	–	0.5	MICA+TRB	0.5+<0.015	Indifferent
CAS	>8	1			
ANID	–	4			
KTC	–	1			
TRB	–	>2			
5FC	>64	–			

AMB, amphotericin B; MON, miconazole; ITC, itraconazole; 5FC, flucytosine; VRC, voriconazole; TRB, terbinafine; CAS, caspofungin; MICA, micafungin; POS, posaconazole; ANID, anidulafungin; KTC, ketoconazole

[a] Obtained by CLSI adapted method based on breakpoints available for pathogenic yeasts, Wadsworth Center Laboratories, Albany NY.
[b] Obtained by M38-A2 CLSI broth dilution antifungal susceptibility testing, University of Texas Health Science Center at San Antonio, South Texas reference laboratories.

(Fig. 1A). Histopathologic examination revealed a dermal nodular infiltrate of neutrophils with surrounding histiocytes, some of which were multinucleated. A periodic acid-Schiff-diastase (PAS-D) stain revealed small, narrow angled, branching hyphae. Wound cultures were positive for mold, subsequently identified as *S. apiospermum*. Identification was based on phenotypic characteristics and sequencing of the intertranscribed spacer (ITS) region, which was compared to reference data available at GenBank using the basic local alignment search tool (BLAST) [4]. The isolate was susceptible to voriconazole and posaconazole, but resistant to amphotericin B, 5-fluorocytosine, itraconazole, and caspofungin using the Sensititre YeastOne kit [5], as shown in Table 1. Other cultures for bacteria and acid-fast bacilli were negative. On day +10, the patient was started on intravenous (IV) voriconazole 6 mg/kg for 1 day followed by 4 mg/kg for 4 days, and he continued on oral voriconazole 200 mg q12 hours as an outpatient. Therapeutic trough levels were measured and maintained in a range of 4–6 mg/L. The prednisone, which had been started on day −60 at a dose of 60 mg, had been tapered to 40 mg at day 0 and was tapered off completely by day +84.

On day +99, the patient was admitted for acute decompensated heart failure. At that time, voriconazole was discontinued given improvement of his left lower extremity lesion. By day +114 (15 days since discontinuing therapy), recurrence of disease was observed with new metastatic nodules in the upper extremities, one of which was incised and drained and again grew *S. apiospermum* with sensitivities and synergy studies shown in Table 1. IV voriconazole was restarted at 6 mg/kg for 1 day followed by 4 mg/kg for 5 days and was continued orally at 200 mg q12 hours as an outpatient. The patient was subsequently