

Cutaneous and Systemic Infection With *Scedosporium apiospermum*

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We present a case of cutaneous and systemic infection with Scedosporium apiospermum occurring in a patient with systemic lupus erythematosus. Scedosporium apiospermum is a rare cause of systemic mycosis but is associated with a high rate of mortality in immunocompromised hosts. Because the patient presented in an advanced state of infection, supportive measures were unsuccessful and definitive diagnosis could not be made until postmortem examination. We discuss the presentation, pathology, diagnosis, and treatment strategies for Scedosporium infection.

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S*cedosporium apiospermum* (asexual anamorph of *Pseudallescheria boydii*) is a rare cause of fungal infection but has a relatively high degree of virulence and can cause severe pulmonary or disseminated infections in immunocompromised patients.^{1,2} We discuss a case of systemic *S apiospermum* presenting as purpura and bullae in an immunocompromised patient with systemic lupus erythematosus and renal failure. We review the presentation, pathology, diagnosis, and treatment considerations for *Scedosporium* infection, as well as prior cases reported in the literature.

Case Report

A 69-year-old woman was transferred to our burn unit for treatment after being found unresponsive at her home with hypotension, decreased mental status, and hemorrhagic bullae with loss of skin on the left arm.

Her medical history revealed nephritis secondary to systemic lupus erythematosus, hypertension with resultant chronic renal failure, acute renal failure secondary to rapidly progressive glomerulonephritis, anemia secondary to chronic renal failure, hyperlipidemia, and coronary artery disease with diastolic dysfunction. Surgical history included carotid endarterectomy, cholecystectomy, and partial colon resection. The patient's current medications included acyclovir, amlodipine, aspirin, prednisone, sodium bicarbonate, and trimethoprim-sulfamethoxazole. Family history and social history were noncontributory. A review of systems revealed only decreased appetite and constipation prior to hospital admission.

Physical examination revealed a temperature of 35.5°C, bradycardia with a heart rate of 56 beats per minute, and relative hypotension (blood pressure, 100/60 mm Hg). There was loss of skin on the left arm; hemorrhagic bullae and purpura with some tearing of the skin on the right arm and hand (Figure 1); purpura on the chest, back, and lower extremities (Figure 2); conjunctival edema; and a grade 2/6 systolic ejection murmur. There were no oral or other mucosal lesions and no target lesions. Nikolsky sign was negative. The differential diagnosis at presentation included gram-negative sepsis, including *Vibrio vulnificus*; toxic epidermal necrolysis; disseminated intravascular coagulation; bullous lupus; and systemic aspergillosis.

Bacterial cultures were negative, and initially fungal cultures also were negative. Blood chemistry studies yielded the following elevated values: creatinine, 1.6 mg/dL (reference range, 0.6–1.2 mg/dL); aspartate aminotransferase, 4625 U/L (reference range, 0–37 U/L); alanine aminotransferase, 1493 IU/L (reference range, 0–40 IU/L); creatine kinase, 435 IU/L (reference range, 20–271 IU/L); and troponin I, 18.9 ng/mL (reference range, 0–0.4 ng/mL). Other laboratory tests revealed the following values: albumin, 2.5 g/dL (reference range, 3.5–5.0 g/dL); alkaline phosphatase, 80 U/L (reference range, 30–120 U/L); total protein, 3.6 g/dL (reference

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Figure 1. Right arm (A) and hand (B) with hemorrhagic bullae and purpura.

range, 6.0–8.0 g/dL); phosphorus, 2.2 mg/dL (reference range, 2.3–4.7 mg/dL); and magnesium, 1.6 mEq/L (reference range, 1.3–2.1 mEq/L). The patient's white blood cell count was 20,800/ μ L (reference range, 4500–11,000/ μ L), hemoglobin level was 10.5 g/dL (reference range, 14.0–17.5 g/dL), and platelet count was 17,000/ μ L (reference range, 150,000–400,000/ μ L). Urinalysis revealed 1+ leukocyte esterase but was negative for nitrate. Further blood analysis revealed antinuclear antibody titer of 1:320 serum dilution; low C3 and C4 levels; no cryoglobulins; no antineutrophilic cytoplasmic antibodies; and no infection with hepatitis A, B, or C virus. Coagulation studies revealed the prothrombin time and partial thromboplastin time to be minimally elevated. Blood cultures were negative for bacteria, though yeast forms were found in the aerobic bottles.

Two skin biopsies were performed. Many branching hyphae and fungal spores were seen with hematoxylin and eosin stain. Special stains demonstrated fungal organisms (Figure 3), with a differential of *Aspergillus*, *Cryptococcus*, or *Fusarium* species. Direct immunofluorescence revealed granular IgG and IgM deposits present at the dermoepidermal junction and in the blood vessels. Heavy fibrin deposition was present in the dermis with some perivascular fibrin, which was suggestive of lupus erythematosus with vasculitis.



Figure 2. Left leg with hemorrhagic bullae and purpura (A). Right leg with bullae, purpura, and ulcerations (B).

The patient's condition rapidly deteriorated. She was unresponsive when she was brought to the hospital and died within 48 hours of admission, despite administration of vasopressors and broad-spectrum antibiotics. On postmortem examination, numerous fungal spores and medium-sized to slender hyphae with branching and septations were seen in the skin, myocardium, lung tissue, bone marrow, thyroid, and kidney. Definitive identification of *S apiospermum* was based on colony and microscopic morphology conducted at our mycology testing laboratory.

Comment

Scedosporium apiospermum is an emerging opportunistic pathogen that can cause various infections in humans. In immunocompetent hosts, localized soft tissue infections, such as mycetoma or osteoarticular infections, are most common and related to *P boydii*, which is the teleomorph of *S apiospermum*. *Scedosporium apiospermum* has a relatively high degree of virulence, particularly in immunocompromised patients, and can disseminate in this population.^{1,2}

The natural environmental habitat of this opportunistic fungus is not definitively known, though it can be isolated from soil, sewage, contaminated water, and manure of farm animals.^{2,4} Human infection most often results from penetrating trauma or surgery, or from inhalation of spores from the environment.⁵⁻⁷ Infection of the skin, soft tissue, bone, and sinuses; pneumonia; keratitis; endocarditis;

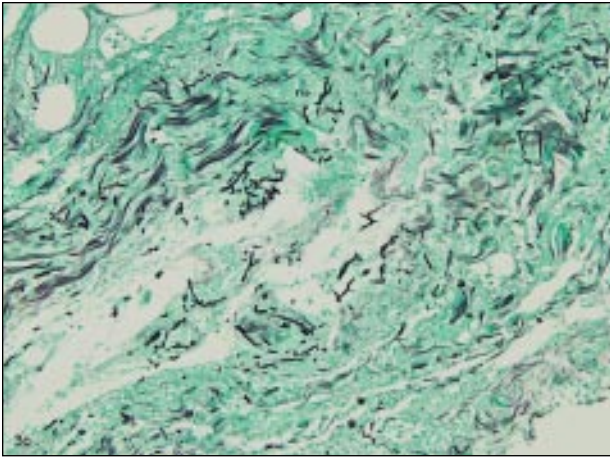


Figure 3. Septate branching hyphae of *Scedosporium apiospermum* (Gomori methenamine-silver, original magnification $\times 200$).

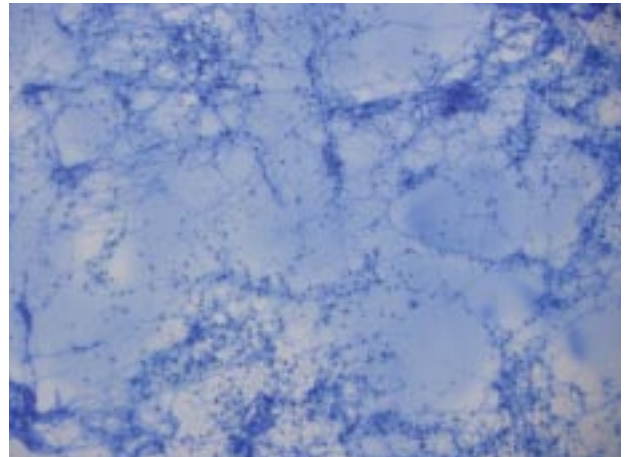


Figure 4. Wet mount of *Scedosporium apiospermum* with thin-branching septate hyphae and yeast forms (original magnification $\times 200$).

white grain mycetoma; lymphadenitis; endophthalmitis; meningoencephalitis; brain abscess; endocarditis; and septic arthritis due to *S apiospermum* have been reported.^{3,4,8-10}

Cutaneous infections by *S apiospermum* may clinically present as solitary ulcers, infiltrative erythematous plaques and nodules, or suppurative nodules and ulcers in a lymphangitic pattern.¹¹ Our patient presented with bullae and purpura reminiscent of systemic aspergillosis.¹ The differential diagnosis of bullae with purpura should include toxic epidermal necrolysis; disseminated intravascular coagulation; systemic aspergillosis; other systemic mycoses including *S apiospermum*; disseminated meningococcemia; staphylococcal scalded skin syndrome; gram-negative sepsis, including *V vulnificus*; other hematologic and clotting disorders; heparin or coumadin necrosis; and (though less likely) bullous impetigo, bullous pemphigoid, fixed drug eruption, lupus, and pemphigus vulgaris.

On microscopic examination, the asexual reproductive structures are seen: septate hyaline hyphae (2–4 μm in diameter), conidiophores, and (annelo) conidia. The conidiophores of *S apiospermum* are simple. Conidia (4 \times 5 to 7 \times 12 μm) are unicellular and oval in shape, and they truncate at their base. The conidia of *S apiospermum* often are formed singly on the conidiophores (Figure 4).²

Typically, *S apiospermum* and its teleomorph, *P boydii*, cause eumycotic mycetoma with granule formation seen on histopathology. The granules are composed of hyaline, septate, and branching hyphae. However, in patients with dissemination, mats of septate hyphae may be observed in the infected tissues. The histopathology of *S apiospermum* is morphologically similar to *Aspergillus* species, which

often leads to misidentification and subsequent delay in initiating appropriate therapy.^{2,3} Serologic cross-reactivity with *Cryptococcus neoformans* and highly polymorphic cultures of *Scedosporium* species are additional barriers to correct identification. Polymerase chain reaction may be used to distinguish *Scedosporium* from *Aspergillus* more rapidly than cultures.¹²

Treatment of *S apiospermum* infections can be problematic because of difficulty identifying the organism and high resistance of *S apiospermum* to most commonly prescribed antifungal agents.⁸ Published minimum inhibitory concentrations have limited predictive value for effective treatment in vivo, and it is anticipated that more virulent and more resistant genotypes will be selected in the course of short-term evolution.² Combination antifungal therapy has not been shown to affect the outcome of *S apiospermum* infection in patients who underwent a solid organ transplant, but further studies are needed.¹³ Surgical intervention usually is required for the treatment of mycetoma caused by *S apiospermum*, and limb amputation often is required for bone involvement. However, successful treatment of localized and disseminated *S apiospermum* infection with voriconazole has been reported.^{9,12,14,15} Because of the high mortality and morbidity associated with *S apiospermum* infection, particularly in immunocompromised hosts, early identification and definitive treatment are critical.

Our patient presented at a late stage of her infection with several comorbidities, making management and diagnosis difficult. However, the presentation of bullae and purpura in an ill patient may indicate fungal infection, particularly by *S apiospermum*, and empiric treatment with an

appropriate antifungal agent should be promptly initiated. When disseminated infection by *Aspergillus* is suspected based on initial culture results, the possibility of misidentification must be kept in mind. If polymerase chain reaction is not an option for definitive diagnosis, the antifungal agent chosen must cover for *S apiospermum* to avoid unnecessary mortality and morbidity. In these patients, voriconazole covers *Aspergillus* well. Polyene macrolide antifungals, such as amphotericin B deoxycholate, remain the first-line drug therapy against *Aspergillus*, while most isolates of *S apiospermum* are resistant to it.^{16,17} Itraconazole is reported to have activity against *Aspergillus* but not *S apiospermum*.^{16,18} In vitro, neither fluconazole nor flucytosine have been shown to have activity against either *Aspergillus* or *S apiospermum*.¹⁸ Of the echinocandins, caspofungin acetate is recommended in the setting of refractory *Aspergillus*, and micafungin sodium, which is fungistatic against *Aspergillus*, is only recommended in salvage (combination) therapy.¹⁶ Echinocandins have in vitro activity against *S apiospermum*, but there are no reports in the literature of its successful use in vivo.¹⁹ In vitro, posaconazole has been shown to have activity against both *Aspergillus* and *S apiospermum*.²⁰

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