



Case Report

Phaeoacremonium parasiticum phaeohyphomycosis in a patient with systemic lupus erythematosus treated successfully with surgical debridement and voriconazole: A case report and review of the literature



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ABSTRACT

A 26-year old woman presented for evaluation of extensive edema, erythema, sinus tract formation and purulent drainage from the left lower extremity after trauma from a wooden object approximately three months prior. Skin biopsies and blood cultures revealed *Phaeoacremonium parasiticum* consistent with a diagnosis of phaeohyphomycosis. Despite hospitalization and initial treatment with several antifungals, including voriconazole, her infection progressed. Surgical debridement with split thickness skin grafting was performed. Subsequent clinical improvement allowed a transition from intravenous to oral voriconazole and discharge home. Seven months post presentation she remained on oral voriconazole with significant improvement and no clinical evidence of recurrence. This case illustrates an approach to management where aggressive debridement with split-thickness skin grafting and a prolonged course of intravenous and oral antifungals resulted in a good long-term outcome for the patient.

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Introduction

The genus *Phaeoacremonium* comprises dematiaceous molds first identified as etiologic agents of phaeohyphomycosis by Ajello et al. in 1974 [1]. *Phaeoacremonium* species are primarily environmental pathogens of woody plants, though some species are known to cause human disease after cutaneous trauma [1]. Cutaneous infection by *Phaeoacremonium* is most often encountered and may lead to dissemination and fungemia, particularly in immunocompromised patients [2]. Recent data have suggested an increasing incidence of phaeohyphomycosis. Cutaneous presentation can be varied and may include subcutaneous nodules, macules, papules, pustules, plaques, eschars and

multiple abscesses, and mycetomas. On review of 39 isolates identified from medical records at the University of Texas M.D. Anderson Cancer Center, 38% had skin lesions and 33% of 39 patients died within three months of diagnosis [3]. Treatment is often complex and includes prolonged use of intravenous and oral antifungals and possibly surgical intervention. We report a case of extensive phaeohyphomycosis secondary to *Phaeoacremonium parasiticum* in an immunocompromised patient that was successfully treated by a multidisciplinary team with antimicrobial and surgical interventions.

Case

A 26-year-old Hispanic woman presented from an outside hospital for evaluation of left lower extremity swelling, erythema, edema, and purulent drainage of three months' duration after trauma to her left leg from a wooden object. Her past medical history was significant for systemic lupus erythematosus (SLE) with stage IV nephritis for which she was treated with prednisone

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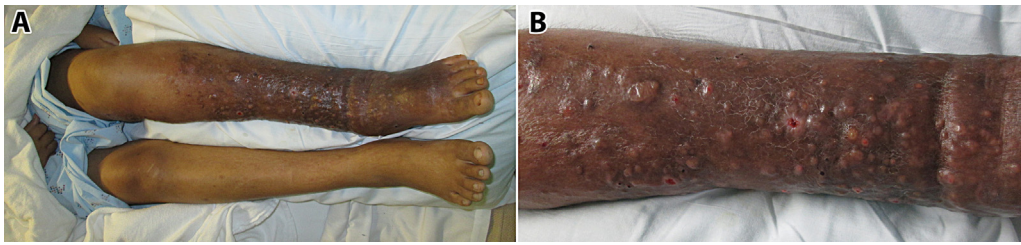


Fig. 1. Examination revealed left lower extremity erythema and edema along with papules, pustules and nodules extending from the left dorsal foot to the left medial thigh (A). Closer examination demonstrated tender papules, some with overlying crust (B).

5 mg daily and mycophenolate mofetil (MMF) 500 mg twice daily at presentation to our hospital. Initially, she was admitted to a local hospital and treated for possible cellulitis with vancomycin and piperacillin/tazobactam and later with numerous antifungals including itraconazole, fluconazole, voriconazole and amphotericin B for approximately one month without improvement.

Physical examination revealed a well appearing, afebrile Hispanic woman in no acute distress. From her left dorsal foot to her left medial thigh there was marked woody induration with numerous warm and tender papules, nodules, and several pustules coalescing into larger plaques with sinus tract formation (Fig. 1A and B). Several areas with purulent drainage and dark brown crust were identified. The left leg was significantly larger and more edematous than the right leg. There was no inguinal lymphadenopathy. Given the patient's immunosuppression, an infectious process was suspected, encompassing clinical concern for fungi and mycobacteria. Skin punch biopsies were therefore taken from the left lower extremity for histopathologic evaluation and culture. Histopathologic evaluation revealed a dense acute inflammatory infiltrate composed of numerous palisading histiocytic granulomas with interspersed giant cells, central neutrophilic microabscesses and lymphocytes extending from the superficial to the deep dermis. Periodic acid-Schiff (PAS) and Grocott Methenamine Silver (GMS) staining revealed numerous septate, hyaline hyphae with acute angle branching consistent with phaeohiphomycosis (Fig. 3A and B).

The patient was evaluated by a multidisciplinary team including infectious disease, dermatology, rheumatology, internal medicine and burn surgery. Magnetic resonance imaging of the left lower extremity and brain along with computed tomography of the chest did not reveal evidence of disseminated disease. Aerobic and anaerobic bacterial and fungal blood and skin cultures were performed and demonstrated *Phaeoacremonium* spp.

Culture of biopsy material revealed small white colonies on Remel potato dextrose agar at 25 °C within 72 h. In slide culture on

cornmeal agar at 25 °C colonies were initially velvety and white-gray and developed gray-brown pigment and clusters of brown aerial hyphae at one week (Fig. 4A and B). A lactophenol cotton blue mount revealed pigmented septate hyphae with brown, cylindrical, slightly tapered conidiophores with clusters of oblong, hyaline conidia consistent with *Phaeoacremonium* species (Fig. 4C). Isolate identification was obtained by D2 large subunit (LSU) ribosomal DNA fungal sequencing [4] at the State Hygienic Laboratory at the University of Iowa. Related sequences deposited in the National Center for Biotechnology Information (NCBI) GenBank [5] were located using BLAST [6]. *P. parasiticum* (NCBI accession no. HE792808) was identified as 99.6% identical to the patient isolate.

Antifungal susceptibility testing was performed at Mayo Medical Laboratories (Rochester, MN) and the University of Texas Health Science Center (San Antonio, TX) utilizing the Clinical Laboratory Standards Institute (CLSI) broth microdilution method M38-A2 [7]. Minimum inhibitory concentration (MIC) endpoints, defined as the lowest drug concentration that prevented discernible growth, were determined at 48 and 72 h. The MICs of amphotericin B, voriconazole, fluconazole, and terbinafine against the patient's isolates of *P. parasiticum* are shown in Table 1. Drug interactions (synergy) studies were performed by the University of Texas Health Science Center using a checkerboard microdilution method [7,8] and testing parameters as described in CLSI M38-A2 and are shown in Table 2.

Surgical debridement was recommended given the lack of improvement with intravenous antifungals. Her immunosuppressive therapy was temporarily held, and she underwent extensive surgical debridement followed by split thickness skin grafting (Fig. 2A and B). She was continued on voriconazole at 200 mg orally twice daily with terbinafine 500 mg three times daily; however, terbinafine was decreased to 500 mg twice daily and later discontinued due to leukopenia and absence of synergistic activity with laboratory testing. Treatment for SLE was later resumed with

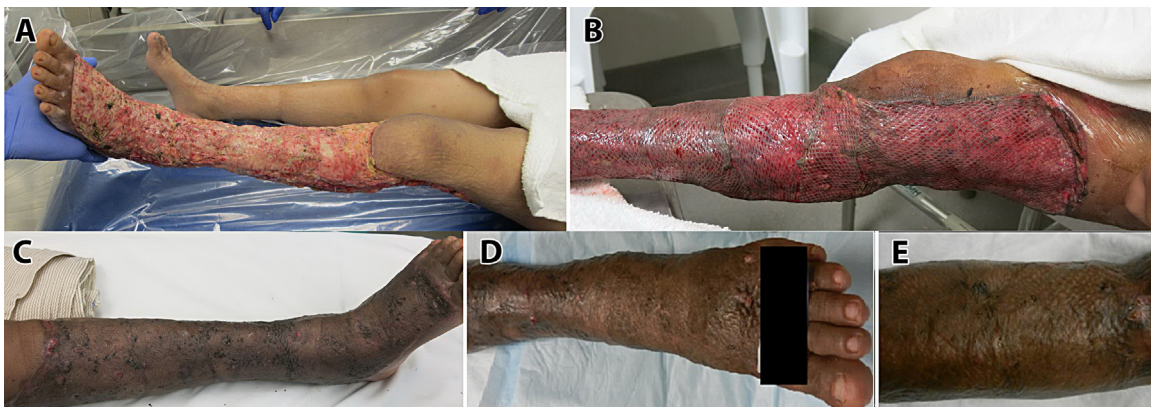


Fig. 2. Physical examination of the left lower leg, two days post-debridement (A). Left lower extremity after placement of split thickness skin graft (B), 3 months (C) and 6 months after follow up (D–E).

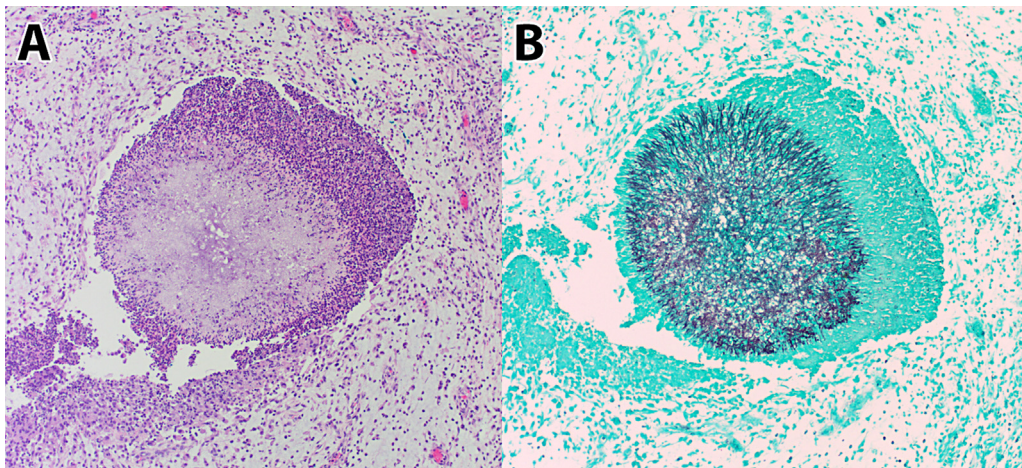


Fig. 3. Histologic sections of the punch biopsy show a dense inflammatory infiltrate and numerous granulomas; staining with PAS (A) and GMS stains (B) revealed numerous septate, hyaline hyphae with acute angle branching. Reproductive structures were not identified.

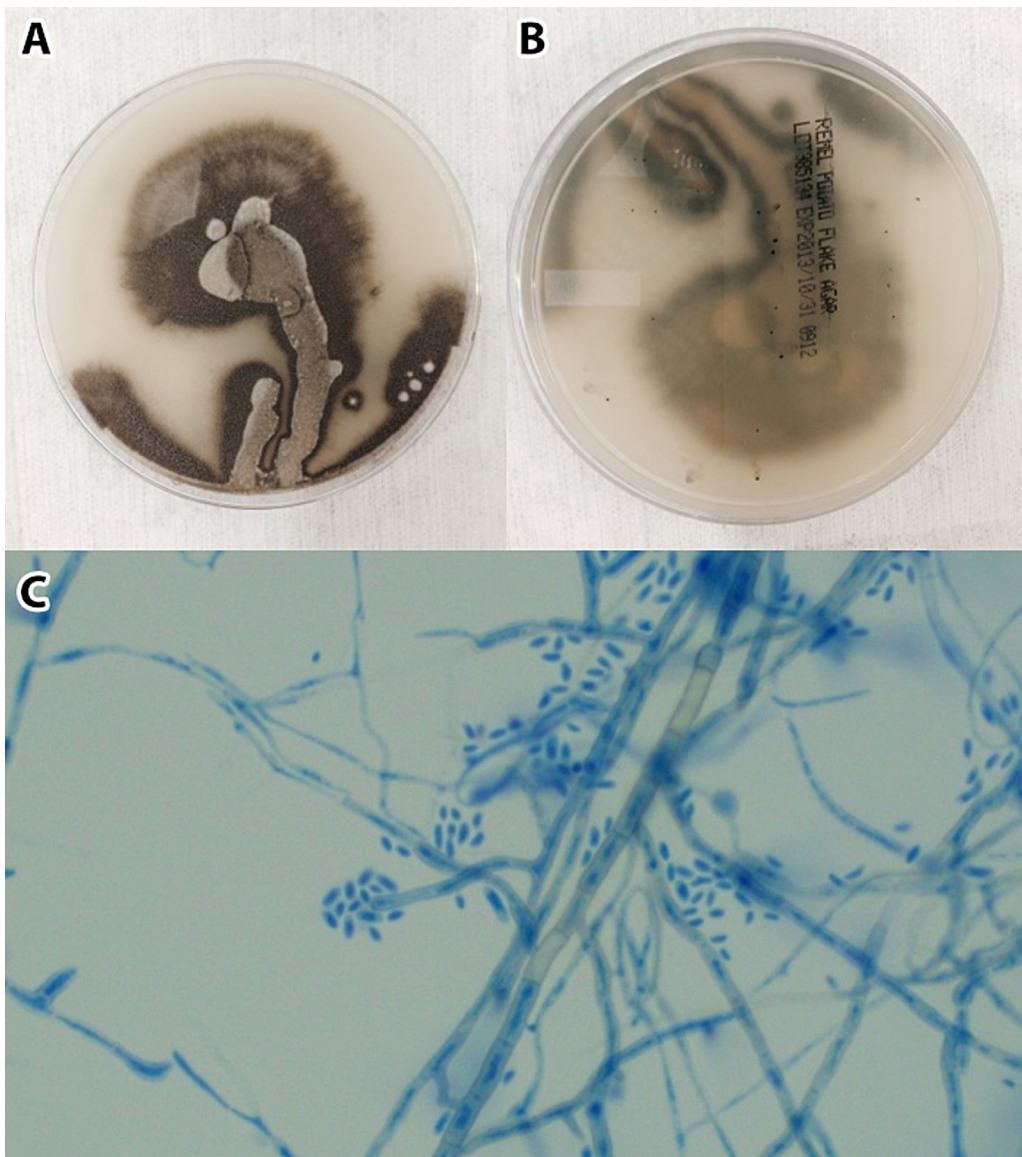


Fig. 4. Pictured are colonies (superior (A) and inferior (B) aspects of culture plate shown) with moderate to slow growth in potato dextrose agar at 25 °C; colonies are low-lying, velvety, and white-gray to brown. Lactophenol cotton blue stain following growth in cornmeal agar for slide culture at 1 week (C) reveals phialides bearing apical clusters of cylindrical, hyaline conidia and brown septate hyphae consistent with *Phaeoacremonium* species.

Table 1
In vitro susceptibilities of *Phaeoacremonium parasiticum* isolate.

Drug	Result (µg/ml)	CLSI M38-A2 interpretation
VORI	0.5	No established guidelines
TERB	0.5	No established guidelines
AMB	1.0	No established guidelines
FLU	>64	No established guidelines

VORI, voriconazole; TERB, terbinafine; AMB, amphotericin B; FLU, fluconazole. MIC endpoints for all drugs are defined as lowest drug concentrations that prevent discernable growth (optically clear) compared to drug-free controls.

prednisone 5 mg daily and hydroxychloroquine 300 mg daily. At follow up seven months later, the patient was doing well with no clinical evidence of recurrence (Fig. 2C–E).

Discussion

P. parasiticum is a ubiquitous dematiaceous mold that rarely causes human infection. This mold was initially reported in 1974 as *Phialophora* and subsequently associated with the *Phaeoacremonium* genus by Crous et al. in 1996 [9]. *Phaeoacremonium* species reported to cause human infection have included *P. parasiticum*, *P. rubrigenum*, *P. alvesii*, *P. krajdienii*, *P. amstelodamense*, *P. griseorubrum*, *P. tardicrescens*, and *P. venezuelense* [2].

Patients presenting with *Phaeoacremonium* infection often have conditions rendering them immunocompromised including hematologic malignancies in the setting of chemotherapy, stem cell transplantation, rheumatoid arthritis treated with infliximab, or adult Still's disease managed with oral prednisolone [3,9–11]. The reported increase in dematiaceous mold infections may be related to the increasing size of the immunosuppressed population. However, there also have been reports of *Phaeoacremonium* infection in healthy adults [2].

Clinically, patients often present after trauma to the cutaneous tissue of the lower extremity, resulting in local inoculation. This may result in nodules, cysts, abscess, or eumycetoma characterized by edema, sinus tract formation, and purulent drainage with grain formation [10]. Possible complications include fungemia, central nervous system infection including brain abscess, endophthalmitis, osteomyelitis, arthritis, cavitary lung lesions, airway colonization, sinusitis and infective endocarditis [3,12].

Antifungal regimens utilized in the management of phaeohiphomycosis due to *Phaeoacremonium* species vary as optimal treatment has not yet been clearly defined; however, good outcomes have been associated with itraconazole, amphotericin B, 5-fluorocytosine, voriconazole, terbinafine, and surgical debridement [12–14]. Azoles, in particular, have been reported to yield good results. Although dematiaceous molds have been increasingly implicated as significant human pathogens, particularly in immunosuppressed individuals, there is little data on *in vitro* antifungal susceptibility and the efficacy of combination drug therapy [13]. An analysis of 381 isolates of filamentous fungi, including eight isolates of *P. parasiticum*, reported favorable *in vitro* activity of voriconazole against *P. parasiticum* (MIC range 0.125–2 µg/ml, mean 0.55 µg/ml) while the MICs of amphotericin B (range 1–16 µg/ml, mean 3.08 µg/ml) and itraconazole (range 0.25–32 µg/ml, mean 6.17 µg/ml) were less favorable [15]. Currently, MIC susceptibility breakpoints have not been established

Table 2
 Synergy of voriconazole and terbinafine against *Phaeoacremonium parasiticum* isolate.

Drugs	Result (µg/ml)	Interpretation
VORI + TERB	0.125 + 0.25	Indifferent

VORI, voriconazole; TERB, terbinafine.

and there is no data correlating MICs with clinical outcome so MIC data should be interpreted with caution [14].

Combination drug therapy has been showed to be effective in the treatment of certain dematiaceous fungal infections. A synergistic reduction in antifungal MICs may be shown with the addition of a second drug that reflects enhanced antifungal activity *in vivo*. *In vitro* synergy has been reported between terbinafine and both amphotericin B and azoles. A recent study by Biancalana et al. investigated the synergistic activity of terbinafine in combination with itraconazole, voriconazole, and amphotericin B in the treatment of various dematiaceous fungal infections (not including *Phaeoacremonium* species). Outcomes showed 100% synergism (29 of 29 isolates) for terbinafine in combination with voriconazole, 96.5% synergism for terbinafine in combination with amphotericin B, and 75.9% synergism for terbinafine in combination with itraconazole. No antagonism was identified [13]. However, as in this case, indifferent synergistic results have also been reported for some dematiaceous fungi [16]. Further research is needed to standardize the roles of combination drug therapy, surgical debridement and other management strategies in patients with phaeohiphomycosis due to *P. parasiticum* and other dematiaceous molds.

Herein, we report a rare and extensive case of phaeohiphomycosis secondary to *Phaeoacremonium parasiticum* in an immunocompromised patient. Clinical and therapeutic success required withdrawal of immunosuppressive therapy, extensive surgical debridement and skin grafting in parallel with a prolonged course of antifungal therapy. Microbiologic identification and susceptibility testing were imperative for appropriate antifungal selection as empiric antifungal regimens for phaeohiphomycosis are not currently well defined [13].

This case report was reviewed and cleared for publication by the Institutional Review Board at the University of Iowa.

Conflict of interest statement

The authors have no relevant conflicts of interest.

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The State Hygienic Laboratory of Iowa, 2490 Crosspark Rd, Coralville, IA 52241 performed initial culture and identification of the mold.

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