Phaeohyphomycosis in a Premature Infant

MAJ Michael G. Bryan, MC, USAF, Lackland Air Force Base, Texas
LTC Dirk M. Elston, MC, USA, Lackland Air Force Base, Texas
CPT Chad Hivnor, MC, USAF, Lackland Air Force Base, Texas
MAJ Beth A. Honl, MC, USA, Lackland Air Force Base, Texas

We present a case of a premature infant who developed a cutaneous infection with a pigmented fungus that subsequently spread systemically. We discuss the diagnosis and management of this difficult condition. Fungal culture is slow and sensitivity testing is technically difficult. Often, therapy must be initiated based on the histologic appearance of the fungus.

Phaeohyphomycosis refers to infection by dematiaceous (dark-colored) fungi and is characterized by pigmented hyphal elements in the infected tissue. Most infections are limited to the skin or subcutaneous tissue. In immunocompromised patients, the fungus may invade deeply and disseminate.

Case Report

A 23-week-gestation female infant was born precipitously after a motor vehicle accident-induced placental abruption. She was resuscitated and placed on a high-frequency ventilator in a supine position. Six days later, she was changed to a conventional ventilator and was turned to a prone position. At that time, she was noted to have several necrotic ulcers on her low back, buttock, and left hip (Figure 1). The dermatology department was consulted to evaluate these "pressure ulcers."

A shave biopsy was performed on one of the buttock lesions after application of topical anesthetic cream (a eutectic mixture of lidocaine and prilocaine). Rapid tissue processing of histologic sections and calcofluor white staining of a tissue homogenate were employed. Hematoxylin and eosin staining of the tissue specimen revealed fungal hyphae with bubbly cytoplasm and thick refractile walls compatible with phaeohyphomycosis.

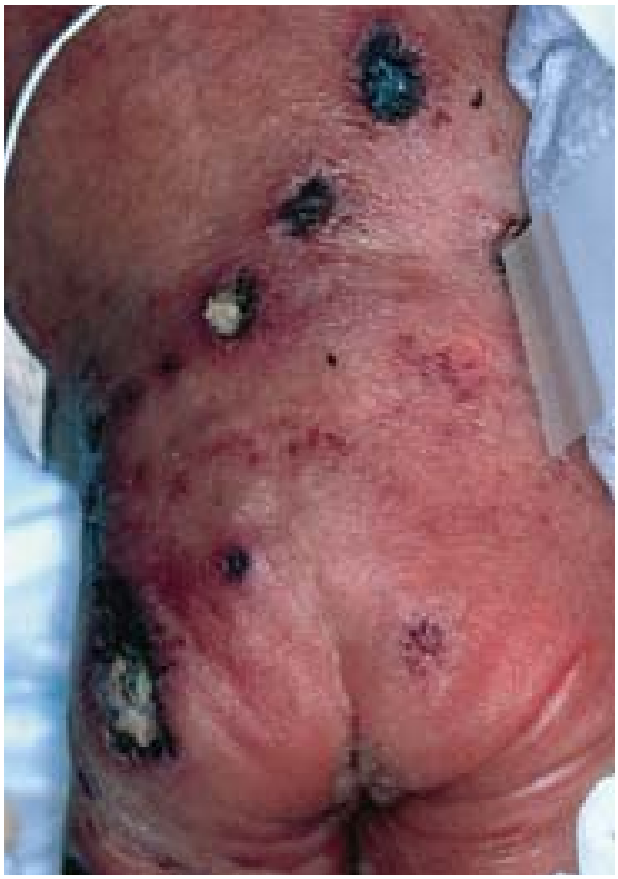

FIGURE 1. Necrotic lesions.

Local débridement was performed by plastic surgery and the patient was started on liposome-encapsulated amphotericin B, 5 mg/kg/day, and itraconazole, 6 mg/day (7.5 mg/kg/day). The excised specimens revealed invasive fungal elements with focal pigment extending to the deep resection margin in the subcutaneous tissue (Figure 2). The patient initially did well

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From Wilford Hall Medical Center, Lackland Air Force Base, Texas.

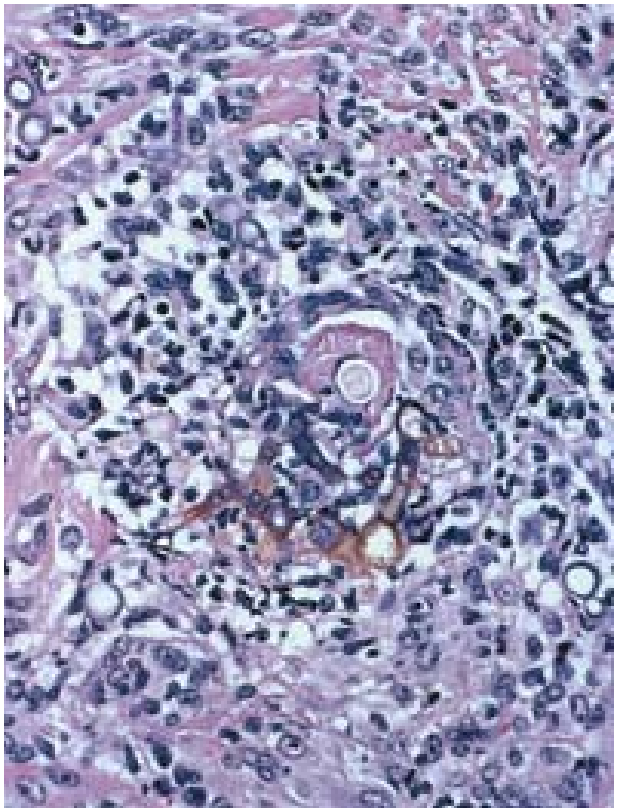

FIGURE 2. Pigmented hyphae (H&E; original magnification, X 200).

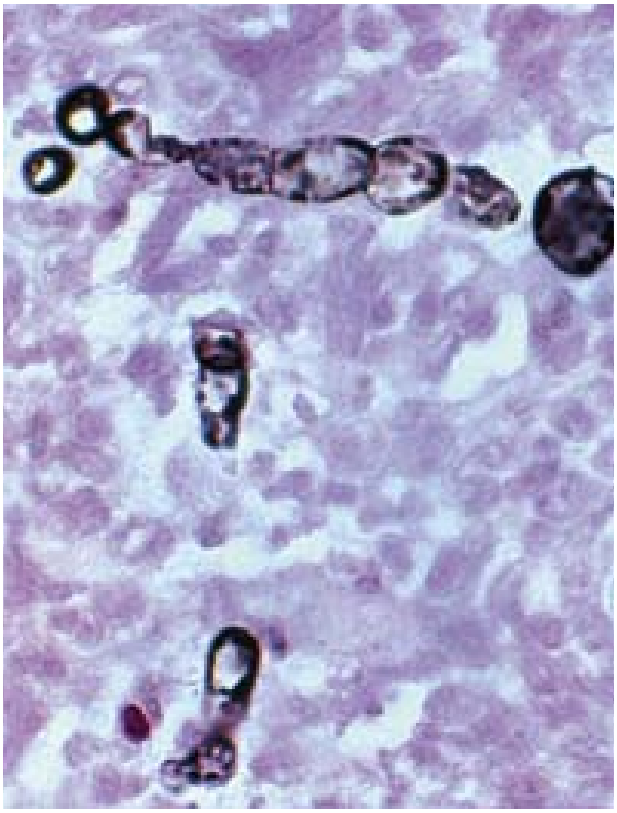

FIGURE 3. Pigment stains as melanin (Fontana-Masson, original magnification, X 400).

with no new lesions and only minimal local extension of necrosis in the débrided areas. These latter foci responded to conservative débridement and continued antifungal therapy. Nine days later, the patient succumbed to cardiorespiratory failure. A post-mortem examination revealed disseminated fungal disease involving the lungs, liver, kidneys, heart, brain, and thyroid. Fungal cultures eventually grew *Bipolaris*.

Comments

Phaeohyphomycotic infections have been categorized into four types: superficial, cutaneous/corneal, subcutaneous cysts, and systemic/disseminated.[1] Superficial infections are limited to the stratum corneum and lack any significant inflammatory response, as in tinea nigra. Keratinized tissue invasion with some degree of host reaction are the features of the cutaneous/corneal infections. Subcutaneous infections are often manifested by mycotic cysts resulting from traumatic implantation of the infecting fungus. Subcutaneous cysts are usually indolent infections in immunocompetent individuals. *Exophiala jeanselmei* is the most common organism. Systemic disease results from dissemination to internal organs from a primary site such as the skin. Invasive disease in immunosuppressed patients is usually caused by *Bipolaris*. The fungus may invade deeply and may disseminate. Despite the potential for systemic spread of these infections, phaeohyphomycosis is primarily a cutaneous disease. Dermatologists must be familiar with this entity and maintain a high degree of suspicion in the appropriate clinical setting to make the diagnosis.

Histologic examination reveals hyphal structures with brown pigment generally visible. The pigment is melanin, and hyphae will stain with a Fontana-Masson stain for melanin (Figure 3). The pigment may be present only focally in histologic specimens. Other morphologic features of the hyphal structures often suggest a phaeohyphomycotic organism and prompt a search for focal pigment. In the case of *Bipolaris*, the most common cause of phaeohyphomycosis, these features include a thick, refractile wall together with ample bubbly cytoplasm.

Fungal culture is notoriously slow, fungal drug sensitivity studies are difficult as well as slow, and few laboratories produce reliable results. Physicians must commonly base initial therapy on the morphologic features of the fungus in tissue sections. Table I[2-10] lists the morphologic characteristics of common fungal pathogens in tissue sections and the best empiric choices for therapy based on a review of the current literature.

Table I.

Drugs of Choice for Invasive Fungal Organisms

Organism	Appearance in Tissue	Best Empiric Initial Therapy
Mucor group *Mucor pusillus* *Absidia corymbifera* *Cunninghamella elegans* *Rhizopus*	Wide, knobby, nonseptate hyphae with thick, refractile walls and inconspicuous cytoplasm. Thick walls appear to be empty. Branching, when visible, is at 90° angle.	Wide excision + AMB[3,4]
Aspergillus	Narrow septate hyphae with thin, delicate walls and conspicuous bubbly cytoplasm. Cytoplasm usually far more conspicuous than wall. Branching, when visible, at 45° angle.	AMB[5]
Fusarium	Similar to *Aspergillus*	AMB[6] (resistance is common)
Phaeohyphomycosis	Pigment within hyphae may be prominent or relatively inconspicuous. Hyphae generally contain bubbly cytoplasm. Wall frequently thick, refractile. (Combination of thick, refractile walls and bubbly cytoplasm suggests possibility of phaeohyphomycotic organism, esp. *Bipolaris*—should prompt diligent search for pigment within hyphal walls and a Fontana-Masson stain.)	Wide excision + itraconazole[2,7]
Chromomycosis *Phialophora verrucosa* *Fonsecaea pedrosoi* *Fonsecaea compactum* *Fonsecaea dermatitidis* *Cladosporium carrionii*	Pigmented, sclerotic bodies are noted in tissue. These bodies divide by fission, septa within dividing spores may be plainly visible.	Itraconazole[8]
N. Am. Blastomycosis *Blastomyces dermatitidis*	Thick-walled, small budding yeast. Within thick, refractile wall dark nucleus is visible—usually off-center. Budding is broad-based and solitary.	Itraconazole (AMB for severe disease)[9-11]
S. Am. Blastomycosis *Paracoccidioides brasiliensis*	Thin-walled budding yeast. Budding is narrow-based and may be multiple.	Itraconazole[9]
Coccidiomycosis *Coccidioides immitis*	Large spherule with basophilic granular cytoplasm. Endosporulation may be present.	Fluconazole/itraconazole (AMB for disseminated or progressive disease, *meningitis: intravenous + intrathecal)[9,10]
Histoplasmosis *Histoplasma capsulatum* *Histoplasma duboisii*	Intracellular yeast with pseudocapsule, within histiocytes. Large, intracellular yeast forms averaging 7 to 15 μm in diameter.	Itraconazole (AMB for severe disease)[9,10]

AMB, amphotericin B

* Itraconazole has shown some efficacy in treating meningitis.

Although phaeohyphomycotic infections have been attributed to 57 genera and 104 species of fungi, the most common etiologic agents are *Bipolaris* and *Exophiala*.[11] Other frequently encountered etiologic agents include *Curvularia, Chaetomium, Phoma, Exserohilum*, and *Wangiella*. Pathogens of the *Bipolaris* genus are soil dematiaceous fungi with a wide geographic distribution and include the species *australiensis*, *hawaiiensis*, and *spicifera*. Several of these fungi, including *Bipolaris hawaiiensis*, appear to have a tendency for neurotropism, causing fatal cerebral infections.[11] *Exophiala* fungi are the most common causes of subcutaneous phaeohyphomycosis. These organisms are soil saprophytes and found ubiquitously in nature. The most frequently encountered species in this genus are *jeanselmei* and *dermatitidis*. They commonly produce solitary lesions on the extremities. It appears that the majority of such infections are a result of a traumatic implantation of the offending organism into the cutaneous/subcutaneous tissue.

Excision provides adequate treatment for subcutaneous phaeohyphomycotic cysts. Invasive disease in immunocompromised patients is a medical emergency. Wide surgical débridement should be performed. Drug therapy of phaeohyphomycosis continues to be problematic. The etiologic agents of these infections are not particularly responsive to conventional antifungal regimens, including miconazole, ketoconazole, and amphotericin B. It is not uncommon to see no response to antifungals or recurrence of infection upon cessation of therapy. For this reason, surgical excision of the affected tissue remains an essential part of treatment. The resection may be followed by antifungal chemotherapy, especially in compromised hosts. Recently, several cases of dematiaceous fungus infections have responded to treatment with itraconazole.[12] The dosages used in these cases were between 100 and 600 mg/day. Initial reports suggest that such a regimen in severely diseased or immunocompromised patients is at least as effective, if not more effective than amphotericin with drug side effects being uncommon and generally mild.

Recent evidence demonstrates *in vitro* sensitivity of dematiaceous fungi to terbinafine, although minimum inhibitory concentrations tend to be higher than those for itraconazole. Further laboratory studies suggest that fluconazole given together with either itraconazole or terbinafine may result in synergism much greater than that usually provided by two-drug therapy.[13]

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