Hospital-acquired phaeohyphomycosis due to *Exserohilum rostratum* in a child with leukemia

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The present study describes a case of cutaneous phaeohyphomycosis caused by *Exserohilum rostratum* in a child undergoing treatment for leukemia. The infection was possibly due to contaminated intravenous dressings and was successfully treated with surgical excision combined with liposomal amphotericin B. Consequently, new infection control policies have been implemented at CHU Sainte-Justine (Montreal, Quebec).

Key Words: *Cutaneous;* Exserohilum rostratum; *Nosocomial; Phaeohyphomycosis*

Une phaeohyphomycose causée par une infection à *Exserohilum rostratum* chez un enfant leucémique

La présente étude décrit un cas de phaeohyphomycose cutanée causée par une infection à *Exserohilum rostratum* chez un enfant traité pour une leucémie. L'infection a peut-être été causée par des pansements intraveineux contaminés et a été traitée avec succès par excision chirurgicale associée à de l'amphotéricine B liposomale. Par conséquent, on a adopté de nouvelles politiques de contrôle de l'infection au CHU Sainte-Justine (Montréal, Québec).

Improvement in the management of neoplastic diseases has led to an expansion of the immunocompromised patient population. As a result, the incidence of invasive opportunistic fungal infections has become the focus of rising observation over the past decade. Although *Candida* and *Aspergillus* species have accounted for the most commonly seen infections (1), unusual fungi have emerged as causative agents of human mycoses (2,3).

Exserohilum species are ubiquitous but rarely pathogenic for human beings. They are encountered in grass or rotting wood and thrive in warm and humid climates. The genus is characterized by its conidia, which are ellipsoidal, distoseptate, and have a protruding and truncate hilum. Three species of *Exserohilum* have been recognized as human pathogens: *Exserohilum rostratum*, *Exserohilum longirostratum* and *Exserohilum mcginnisii*. The most common infections caused by *Exserohilum* species are sinusitis and skin infections, although a few cases of cerebral abscesses, keratitis, osteomyelitis, prosthetic valve endocarditis and disseminated infection have been described (4-7).

CASE PRESENTATION

A three-year-old boy newly diagnosed with standard risk acute lymphoblastic leukemia (ALL) was admitted to CHU Sainte-Justine (Montreal, Quebec) to undergo induction chemotherapy. While severely neutropenic, the patient developed a fever of unknown origin for which an empirical broad-spectrum antibiotic regimen was progressively initiated (ticarcillin-clavulanate, tobramycin, vancomycin and metronidazole). On the day his neutrophil number recovered (after having been less than 0.5×10^9/L for 21 days), he presented with a single painless necrotic lesion on his left forearm, which increased rapidly in size to 5 cm in diameter within 24 h (Figure 1). This lesion occurred at the site where a skin abrasion, due to a gauze-covered wood splint used to secure an intravenous line, had been noted the day before. The patient had not left the hospital premises over the previous three weeks. He was afebrile and otherwise asymptomatic. He was still receiving antibiotics and high-dose prednisone (40 mg/m^2/day). The computed tomography (CT) scan of his sinuses revealed bilateral maxillary opacities, but his cerebral, chest and abdominal CT scans remained normal. Ophthalmological examination was also normal.

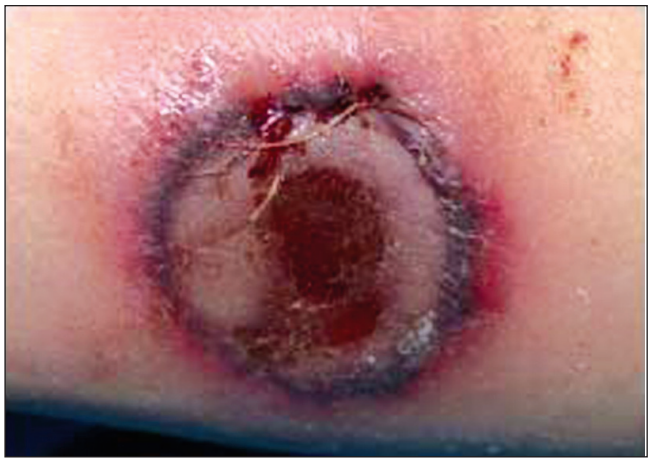

Figure 1) *Cutaneous necrotic lesion on the patient's left forearm*

The patient underwent a skin biopsy of the lesion followed by complete surgical resection. He required a partial thickness skin graft. Grocott stain of the skin showed deep ulcers with filamentous fungi in the blood vessels and subcutaneous tissues

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TABLE 1
Review of primary cutaneous skin infections due to *Exserohilum* species

Patient (reference)	Age (years)/ sex	Predisposing condition	Clinical presentation	Therapy	Outcome
1 (12)	3/M	ALL, neutropenia, intravenous site	Necrotic cutaneous lesion	AmB + 5-fluorocytosine	Cure
2 (13)	8/M	ALL, neutropenia	Ecthyma gangrenosum, sinusitis, pulmonary infiltrates	AmB + itraconazole + surgery	Cure; death (fusariosis) two months later
3 (10)	35/F	Heart transplantation	Cutaneous nodules	Surgery, AmB then ketoconazole	Delayed cure
4 (14)	63/M	Systemic steroids + diabetes mellitus; farmer, local trauma	Nodules, scales	Ketoconazole	Partial improvement; unrelated death at three months
5 (14)	61/M	Topical steroids, psoriasis	Brown plaques	Topical bifonazole	Cure
6 (3)	74/M	Steroid-dependent COPD, infiltrated intravenous site	Hemorrhagic vesicles	Ketoconazole + clorimazole	Cure
7 (15)	40/F	Apparently healthy, bidimaker	Chronic necrotic skin lesion	None	Lost to follow-up
8 (16)	55/F	Apparently healthy, jellyfish sting	Hemorrhagic vesicles and nodules	Ketoconazole + surgery	Cure
9 (17)	22/M	Local trauma, cocaine abuse	Hemorragic bullae	AmB	Unknown; death (hypotension)
10 (present case)	3/M	ALL, neutropenia, intravenous site	Acute necrotic skin lesion	AmB + surgery	Cure

ALL Acute lymphoblastic leukemia; *AmB Amphotericin B; COPD Chronic obstructive pulmonary disorder; F Female; M Male*

and normal fascia. The hyphae were described as septate, and branched at 45° and 90° angles. At 48 h, cultures of the subcutaneous tissue on sheep blood agar and inhibitory mold agar grew rare brown mold colonies. Felty olivaceous colonies grew on potato dextrose agar. Our isolate was subsequently identified as *E rostratum* at the Laboratoire de santé publique du Québec (Montreal, Quebec), due to its conidia with mostly distosepta (7-9) and prominent dark basal and distal septa (8-10). Antifungal susceptibility testing was performed with a microdilution technique according to the guidelines of the Clinical and Laboratory Standards Institute (USA) (formerly The National Commmittee for Clinical Laboratory Standards) (11). The minimal inhibitory concentrations (MICs) for the patient's strain were 1 µg/mL for amphotericin B; 0.12 µg/mL for itraconazole and 2 µg/mL for voriconazole.

Surgical maxillary sinus drainage yielded thick, white pus with a moderate growth of *Moraxella catarrhalis* as pure culture and no growth of fungus. Bacterial and fungal blood cultures (Peds Plus/F and Mycosis IC/F bottles in the BD BACTEC [USA] 9000 system) remained negative. Environmental cultures did not yield any *E rostratum*.

In addition to total surgical resection, the patient was treated with amphotericin B deoxycholate (1 mg/kg/day) for four days followed by liposomal amphotericin B (5 mg/kg/day) because of infusion-related side effects. During consolidation chemotherapy, he experienced several episodes of febrile neutropenia without any sign of relapse of his skin infection. It was then decided to stop antifungal therapy after a total of 110 days. During the subsequent 18 months of maintenance chemotherapy, no antifungal treatment was given and no recurrence of infection was observed.

DISCUSSION

To our knowledge, only nine cases of primary cutaneous skin infections due to *Exserohilum* species have been reported in the English literature (3,10,12-17) (Table 1). Of these, one occurred in a three-year-old child with ALL at the site where cloth tape and a board were used to secure an intravenous line (12). Another pediatric case presented in an eight-year-old boy with ALL who developed febrile neutropenia with ecthyma gangrenosum, sinus and pulmonary involvement. He responded well to a concurrent treatment of liposomal amphotericin B and itraconazole combined with surgical resection of skin lesions (13).

Of the seven adults described, four were immunocompromised. Among them, a 35-year-old woman was a postheart transplant patient. She responded only partially to various antifungal agents; surgical excision of the lesions was necessary (10). Three male patients (3,14) older than 60 years of age were being treated with steroids for various medical conditions. For all patients, a skin break was documented at the site of infection a few days before the appearance of the cutaneous lesions.

Three other cases were described in 'apparently' healthy patients. In India, a 40-year-old female bidimaker (traditional cigarettes) had chronic necrotic plaques on her forearm. She was lost to follow-up before any treatment was instituted (15). A 55-year-old woman developed hemorrhagic vesicles two weeks after a probable jellyfish sting. She responded well to six weeks of ketoconazole and surgical excision (16). Finally, a 22-year-old man was admitted for a cocaine overdose and developed multiorgan failure. He presented with hemorrhagic bullae at the site of superficial lacerations inflicted in a wooded area one week before. The cultures grew *E rostratum* and *Curvularia* species. The authors gave no details about the skin outcome or the HIV status of the patient (17).

Limitations to these reports are the incomplete data on follow-up and the lack of discussion on the potential use of newer antifungal molecules in the setting of phaeohyphomycosis infections. Nevertheless, the mainstay of treatment of cutaneous *Exserohilum* infections is aggressive surgical debridement or excision (1,6) combined with antifungal therapy. The MICs usually show sensitivity to amphotericin B, itraconazole and terbinafine (12,18), and resistance to 5-fluorocytosine and ketoconazole (12). No specific MIC were found in the literature for the echinocandins, but they are available for other dematiaceous fungi such as *Exophiala jeanselmei* and *Alternaria* species which are susceptible in vitro to caspofungin (19). Anidulafungin showed good activity against *E jeanselmei* (20), variable activity against *Bipolaris* species and no activity

against *Alternaria* species. (20,21). Whether these data could be extrapolated to *Exserohilum* species is unknown. No published information was found on the use of echinocandins for phaeohyphomycosis. Historically, amphotericin B is considered the drug of choice for *Exserohilum* infections. There is limited clinical experience reported with azoles, but voriconazole seems very promising from in vitro data and low MICs (22). In a recent case report (7), a young immunocompromised patient with an invasive *Exserohilum* sinusitis was treated with amphotericin B. Voriconazole was used in adjunct on day 5 but it had to be discontinued after 14 days because of an elevation of hepatic transaminases. On day 50, itraconazole was also added. The patient never experienced immune recovery and died on day 64, with a persistent fungal sinusitis but without extension of the disease (7). In another report (23), a child with ALL, suffering from acute *Exserohilum* sinusitis and pulmonary nodular lesions of unknown etiology, did not improve after nine days of amphotericin B treatment. Voriconazole was added and rapidly used as monotherapy. After six weeks of this regimen, there was complete healing of the nasal mucosa and improvement of the chest CT scan. Oral voriconazole was continued for an additional three months and reinstituted during periods of neutropenia without relapse (23). Voriconazole was also used as rescue therapy for invasive alternariosis in a child, with partial success (24). Unfortunately, this drug was not available in Canada at the time our patient presented with his symptoms. For our patient, an aggressive surgical approach and home-administered liposomal amphotericin B were used with good clinical outcome and no side effects.

Although our patient's intravenous dressings were not available for microbiological testing, several cultures taken from the patient's room as well as from the ward were negative for *Exserohilum* species. These specimens included nonsterile tape and gauze, wooden intravenous boards, scissors and boxes that contained care material. Nevertheless, this infection was nosocomial because it occurred after three weeks of hospitalization. A skin break due to the board preceded the patient's fungal lesion. Moreover, the nature of the pathogen recovered is suggestive of an environmental contamination. Cases of nosocomial fungal infections linked to contaminated care material, especially cloth tape (25,26), adhesive tapes or wooden devices (2) are reported in the literature. Because they could be a threat to our immunocompromised patient population, we decided as an infection control policy, to replace all wooden boards used to secure intravenous lines with Plexiglas covered with sterile gauze. We believe that simple environmental control measures such as the one we implemented, as well as special attention to skin care in hospitalized patients, may be potentially lifesaving.

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