Subcutaneous Phaeohyphomycosis in a Renal Transplant Recipient Successfully Treated with Voriconazole

Christian Grønhøj Larsen[1], Maiken Cavling Arendrup[2], Elizabeth Krarup[3], Michael Pedersen[4], Søren Thybo[5] and Frederik Grønhøj Larsen[1]

[1]Department of Dermatology, Copenhagen University Hospital, Gentofte Hospital, Niels Andersens Vej 65, DK-2900 Hellerup, [2]Unit of Mycology and Parasitology, Statens Serum Institut, Departments of [3]Nephrology and [4]Clinical Microbiology, Copenhagen University Hospital, Herlev Hospital, and [5]Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark. E-mail: fregro01@geh.regionh.dk
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Sir,

Phaeohyphomycosis is a rare cutaneous, subcutaneous or systemic infection caused by a range of dematiaceous moulds. *Alternaria*, which is frequently found in soil, polluted water and decaying vegetation, is among the causing organisms (1, 2). Infection due to *Alternaria* species tends to occur most frequently in immunocompromised patients (3), especially in organ transplant recipients (4). The subcutaneous form of phaeohyphomycosis is most prevalent in the rural population of tropical and sub-tropical areas, and usually arises following minor trauma or from walking barefoot on infected soil. It might not become troublesome until many years after the causal injury. The diagnosis is often delayed, as it is frequently unsuspected. Optimal therapy for chronic subcutaneous alternariosis is unknown. This report describes a case of *A. alternata* infection in an immunosuppressed patient and its successful outcome following voriconazole treatment.

CASE REPORT

A 43-year-old man born in Somalia, but resident in Denmark since 1989, received his first kidney transplantation in 1998. The post-transplant course was complicated by chronic rejection leading to haemodialysis and graft removal in 2005. During this time immunosuppressive therapy combined azathioprine, cyclosporine and prednisone. A second kidney was grafted in January 2008 with return of complete renal function. His initial immunosuppressive regime included mycophenolate mofetil, tacrolimus, and prednisone, but 5 months later the former drug was substituted with azathioprine. A few weeks after transplantation he developed two swellings on his lower right leg. He was referred to the Department of Dermatology in August 2008. Physical examination revealed a 110 × 60 mm verrucous tumour at the lateral site of the right foot (Fig. 1A) and an abscess 20 × 30 mm with numerous sinuses located just below his right knee. Skin biopsy of the latter lesion resulted in drainage of viscous yellow pus. No grains were visualized in the pus. On palpation the tumours were soft and painless. There was no regional lymphadenopathy and no fever. Our patient had not left Denmark for the last 19 years, except for a 2-week holiday in Egypt in 2006. He denied any trauma to his foot or walking barefoot outdoors.

Among routine investigations, white blood counts, C-reactive protein, liver enzymes, s-creatinine were normal, but a haemoglobin level of 7.6 mmol/l (range 8.0–11.0 mmol/l) was found. An X-ray of the affected extremity showed no sign of osteolysis or periosteal reaction. At the initial visit a 3-mm punch biopsy was aseptically obtained from each lesion and specimen were sent for histopathological study and bacterial, mycobacterial and fungal cultures. A dematiaceous mould was cultured on Sabouraud agar. Morphologically the hyphae and conidia from the isolate were identified as *Alternaria* sp. by bright-field microscopy. A second tissue biopsy also aseptically obtained confirmed the identification.

Fungal cultures yielded rapidly growing mould, which was identified as *A. alternata* by conventional identification techniques (macro and micromorphology) (5). The identification of one of these isolates was confirmed by sequencing using ITS 1 (forward primer) (5'-CGT AGG TGA ACC TGC GG-3') and ITS 4 (reverse primer) (5'-TCC TCC GCT TAT TGA TAT GC-30). These primers amplify the intervening 5.8S ribosomal DNA (rDNA) and the adjacent internal transcribed spacer 1 (ITS 1) and ITS 2 regions of fungi.

Histological examination of the biopsies taken from both lesions revealed a sinus lined with squamous epithelium. Numerous neutrophils were present in the epithelium and in the surrounding connective tissue, together with lymphocytes and histiocytes. Microorganisms (grains) were not observed.

Oral voriconazole treatment 400 mg twice daily for 3 days followed by 200 mg twice daily was initiated in October 2008 (Fig. 1A) and discontinued after 5 months under due observation and fine-tuning of the tacrolimus dosage. At this point, the lesions had resolved and the subcutaneous induration decreased dramatically (Fig. 1B). Treatment with voriconazole was well tolerated.

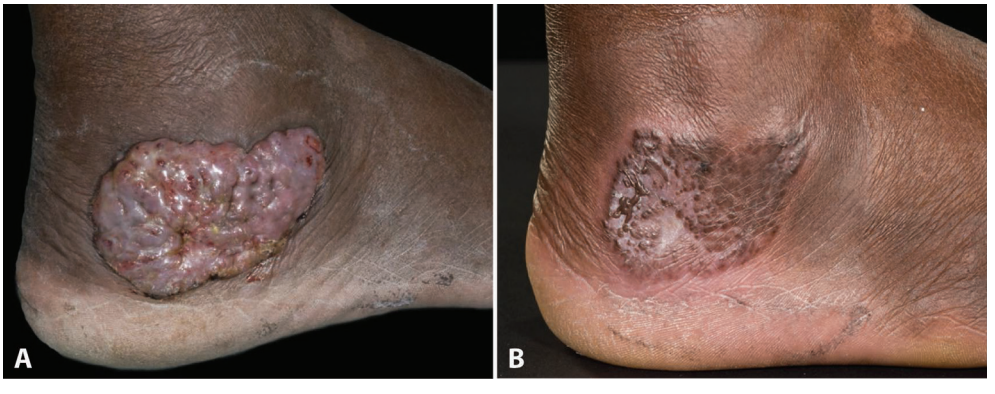

Fig. 1. Clinical feature of subcutaneous phaeohyphomycosis. (A) Before treatment; (B) after 5 months of voriconazole treatment.

DISCUSSION

More than 100 fungi have been reported as agents of phaeohyphomycosis (6) including *Bipolaris*, *Curvularia*, *Exophiala, Exserohilum*, and *Alternaria* most frequently involved in human infections (7). Among members of the last genus, the most commonly found species is *A. alternata*. Phaeohyphomycosis caused by this species may be difficult to recognize because lesions are variable in size and characteristics, ranging from crusted lesions to subcutaneous nodules. The sites affected most commonly are those that are exposed, and it is thought that infection is via traumatic implantation. Most reports of pathogenic *Alternaria* infection occurs in systemic illness or during immunosuppressive therapy (3). The experience of kidney transplantation includes sporadic cases of pheohyphomycosis (4, 8) as chromoblastomycosis agents are more often described (1). Mycetoma is a clinical syndrome characterized by tumefaction, draining sinuses and granules or grains. The diagnosis is established by identifying the type of grains found in the discharge. However in our patient no grains were visualized from the pus, and histopathology revealed no fungal elements using haematoxylin-eosin stain. The possibility of *A. alternata* as a contaminant was considered, but was unlikely, as the same species was isolated on two separate occasions from aseptically obtained biopsies with a one-month interval. The patient was born in Somalia, but had been in Denmark for the last 19 years at the time of presentation. *A. alternata* is a cosmopolitan mould found in soil and on living and dead plants. Thus, whether the present infection was acquired in Denmark, or represents a reactivation of latent infection acquired in his home country due to the immunosuppressive regime, is unknown.

Renal transplant recipients are at increased risk of invasive fungal infections. Despite advances in immunosuppressive therapy, infection remains a leading cause of morbidity and mortality in those patients. Approximately 70% of severe infectious complications occur within 3 months of transplantation (9). During his first period of renal transplant from 1998 to 2005, our patient experienced no clinical signs of any opportunistic infection. Following his second kidney transplantation cyclosporine was substituted with tacrolimus, which is a more potent immunosuppressive agent. It is not known whether tacrolimus-treated patients exhibit a greater risk of deep fungal infection than patients receiving other immunosuppressive regimens, but this has been debated (10).

Optimal treatment of phaeohyphomycosis often includes surgical excision combined with antifungal therapy for several months. Itraconazole has been found to exhibit *in vitro* activity against *Alternaria*, but treatment failures with the compound have been reported (11). Both amphotericin B (12) and fluconazole (13) have been used in the treatment, sometimes with only partially response. Voriconazole has been shown to be an efficient alternative to amphotericin B and surgical debridement for the treatment of cutaneous *A. alternata* infection in a liver transplant patient (14). In the present case a dramatic effect was observed following a few months' voriconazole monotherapy. As more potent immunosuppressive drugs become available to prevent graft rejection, survival increases, expanding the population of immunocompromised patients and increasing the number of patients with opportunistic infections involving the skin (15).

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