Relapse of Cutaneous *Alternaria infectoria* in a Renal Transplant Recipient after 2 Years

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Sir,

Alternaria species are ubiquitous dematiaceous fungi that are occasionally aetiological agents of phaeohyphomycosis. They are commonly isolated from soil, air and plants, but human infections are rare. Cutaneous infections are the most frequent disease caused by *Alternaria* spp. in immunocompromised patients, but rarely also in otherwise healthy hosts. Lesions usually appear on exposed sites, preferentially involving the face, dorsum of the hands, forearms, knees and legs. Verruciform and eczematous skin lesions, papules and plaques, pustules and crusts, chronically vegetating tumorous infiltrates and multiple ulcerating lesions have been documented in the literature (1, 2). Diagnosis is based on histological examination, which reveals hyphae and round-shaped fungal cells in a granulomatous dermal infiltrate, and on identification of the moulds when biopsy fragments are cultured on Sabouraud-dextrose agar without cycloheximide. Since *Alternaria* can be isolated on normal human skin or as a laboratory contaminant, its involvement in human infection must be verified by histological evidence of its presence in tissue. The course of alternariosis in immunosuppressed patients is very capricious, and the treatment is not yet well established. Relapse can occur after even prolonged treatment and long-term follow-up after clinical resolution is advised (2). Among the members of the *Alternaria* genus, the most common isolated species is *A. alternata* but we report here a case of cutaneous infection in a renal transplant recipient caused by *A. infectoria*, which has rarely been reported as a human pathogen before.

CASE REPORT

A 58-year-old man was referred to our department with a 3-month history of several cutaneous lesions on both legs. He had undergone a kidney transplantation 15 months prior to being seen and immunosuppression had been maintained with tacrolimus, mycophenolate mofetil and prednisone since then.

One year after the transplant, he developed a nodule on his left leg and several days later developed papules and nodules on both legs. At the time of presentation there were multiple reddish-brown papules and vegetating masses with smooth surfaces over both legs extending to the ankles (Fig. 1). They were painless and asymptomatic and there was no history of trauma or inoculation.

A skin biopsy showed hyperkeratosis and pseudoepitheliomatous hyperplasia of the epidermis. The dermis showed several microabscesses with a mixed cell granulomatous infiltrate containing neutrophils, lymphocytes, plasma cells, histiocytes and giant cells. Numerous round-shaped fungal cells and septate hyphae were present both within giant cells and extracellularly (Fig. 2). These structures, which appeared hyaline in haematoxylin and eosin (H&E)-stained preparations, were stained deep red with the periodic acid-Schiff stain and black with a Grocott methenamine silver stain. Cultures of the biopsy specimen yielded *Alternaria* species. Imaging studies to rule out internal focus of infection were done, with negative results.

The patient was started on itraconazole orally at an initial dose of 400 mg daily. Partial healing of the lesions was achieved after 4 weeks. However, interaction with tacrolimus was observed with nephrotoxic effect and itraconazole was withdrawn. Treatment was then continued with cryotherapy, double freeze-thaw cycle of 15 s duration, of multiple slightly nodular lesions on four visits. The time between treatment visits was approximately 3 weeks. Some improvement was noted but relapse was observed after discontinuation of treatment.

Oral terbinafine at a dose of 250 mg daily was commenced but no improvement was achieved after 3 months and new lesions were observed on the right arm. Terbinafine therapy was discontinued, and treatment with fluconazole at a dose of 100 mg daily was instituted and continued for a total of 4 months. The tacrolimus dose was decreased to avoid interaction with fluconazole. Slow improvement was noted and complete resolution with residual hyperpigmentation was observed at the end of therapy. However, recurrence of one lesion was noted on the right leg 2 years later. Surgical excision of the lesion was performed. Numerous round-shaped fungal cells and septate hyphae were present in the dermis and cultures of the cutaneous excision specimen yielded *Alternaria* species.

Identification of the causative organism as *A. infectoria* (by the Mycology Laboratory Reference Center of Majadahonda, Madrid) was achieved by sequencing the rDNA internal transcribed spacer (ITS) domain and comparison with other ITS sequences taken from strains maintained in the Centraalbureau

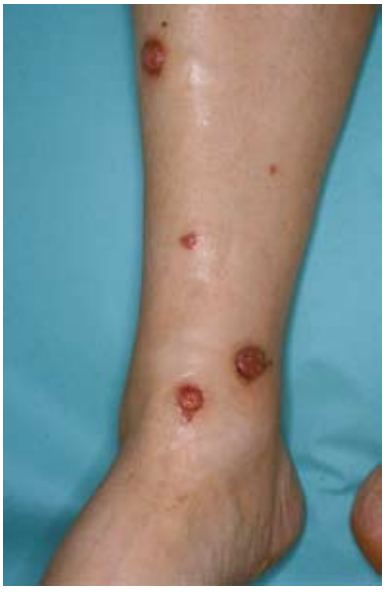

Fig. 1. Multiple reddish-brown papules and vegetating masses with smooth surfaces over both legs.

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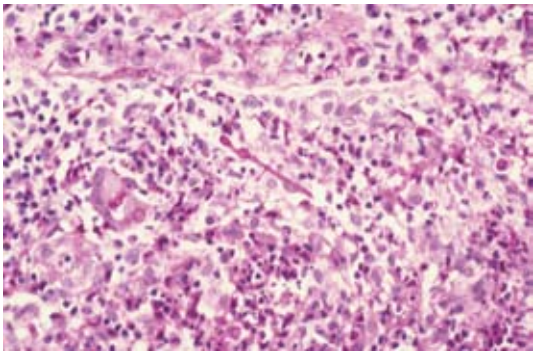

Fig. 2. Skin biopsy showing round-shaped fungal cells and septate hyphae both within giant cells and extracellularly (periodic acid-Schiff stain, original magnification ×400).

voor Schimmelcultures (CBS) reference collection. At the present time, the patient is free of lesions 2 years after the surgical excision.

DISCUSSION

More than 100 fungal species have been documented as agents of phaeohyphomycosis. The genera most frequently involved in human infections include *Bipolaris, Curvularia, Exserohilum* and *Alternaria*. Among the members of the latter genus, the most commonly found species is *A. alternata*. To our knowledge, *A. infectoria* has been found to cause cutaneous lesions in a few cases (3–6).

The treatment of cutaneous *Alternaria* infection is not standardized. Reduction of immunosuppression when possible can be sufficient to treat the lesions. In patients with small and non-numerous lesions, local excision is recommended. When complete excision or reduction of immunosuppression is not possible, oral ketoconazole, itraconazole, fluconazole or terbinafine are possible alternative treatments to amphotericin B (7). However, optimal antifungal dosages and duration of therapy have not been standardized. In addition, the role of *in vitro* susceptibility testing may not be predictive of clinical responsiveness. Itraconazole is suggested to be the drug of choice (in dosages ranging from 100 to 600 mg/day), especially in recognition of its low toxicity (2), but there have been previous reports of itraconazole failure (2, 8–10). There are a few reports of the treatment of *Alternaria* infections with fluconazole (11–13) and terbinafine (14). In spite of the recommendation of oral antifungals in the treatment of cutaneous alternariosis, there have been recent reports of transplant patients successfully treated with lipid formulations of amphotericin B (2, 8, 10).

Treatment with cryotherapy has been successfully used for treatment of multiple lesions of cutaneous alternariosis (15). In our case, despite some improvement in the lesions at the beginning of therapy, relapse was observed after discontinuation of treatment.

Laumaillé et al. (3) reported a case of cutaneous *A. infectoria* infection after liver transplantation with a recurrence 5 months after surgical excision. Our case is exceptional because the recurrence was discovered 2 years after the complete resolution of the lesions.

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