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Sporotrichoid phaeohyphomycosis due to *Alternaria infectoria*

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Summary We describe a cardiac transplant patient who had human cutaneous alternariosis with a sporotrichoid distribution of skin lesions. In this patient identification of the causative organism *Alternaria infectoria* was achieved by sequencing the rDNA internal transcribed spacer domain. Treatment with itraconazole led to clinical resolution within 4 months.

Key words: *Alternaria infectoria*, internal transcribed spacer, itraconazole, molecular biology, sporotrichosis

Species of the genus *Alternaria* and their relatives are often referred to as dematiaceous fungi because of their brownish to olivaceous appearance due to melanin deposition in the cell wall.[1] As plant-inhabiting saprobes they are ubiquitous in the environment and are characterized by a distinctive dermatotropism. To attain pathogenicity for humans, however, further predisposing factors are required.[2,3]

Case report

A 60-year-old female hobby gardener developed a reddish nodular skin lesion on the little finger of her left hand. Within 4 weeks additional skin lesions appeared on the back of the left hand and on the left elbow. She did not recall any preceding trauma. Five years earlier, after the patient had developed a post-myocarditic cardiomyopathy, a heart transplantation was performed. As a result she was receiving long-term treatment with tacrolimus 0·5 mg daily, mycophenolate mofetil 1000 mg daily and prednisolone 8 mg daily.

On examination, there was a scaly erythematous plaque (Fig. 1), 0·8 cm in diameter, on the dorsal aspect of the little finger of the left hand. Firm erythematous dermal nodules were detected on the back of the left hand (Fig. 2) and on the left elbow, each 1·0 cm in diameter.

Histology showed a dense, predominantly histiocytic dermal infiltrate with histiocytic giant cells. Periodic acid-Schiff and Grocott staining demonstrated diffusely distributed fungal elements in the dermis (Fig. 3). At higher magnification, thick-walled budding cells and spheroidal bodies were detected (Fig. 4), some of which were located in the cytoplasm of histiocytic cells and giant cells. Fontana–Masson staining was negative.

On Sabouraud's dextrose agar, rapidly growing, yellowish-white colonies with an olive-green under-surface were demonstrated, suggesting the presence of a dematiaceous fungus. Conidia were not detected, thus hampering direct species differentiation. This was subsequently performed by sequencing of the internal transcribed spacer (ITS) domain of the rDNA gene as described by de Hoog and Horré.[4] Comparison with similar sequences held at the Centraalbureau voor Schimmelcultures (CBS) led to the identification as *A. infectoria* Simmons. The sequence was fully identical to that of the type strain CBS 310.86, and had two base substitutions compared with another reference strain, CBS 308.53, deposited by E.G.Simmons. Subsequently, some conidiation was obtained by repeated transfer on water agar; conidia exhibited the expected morphology of this species. The strain was enlisted in the CBS culture collection as CBS 102692.

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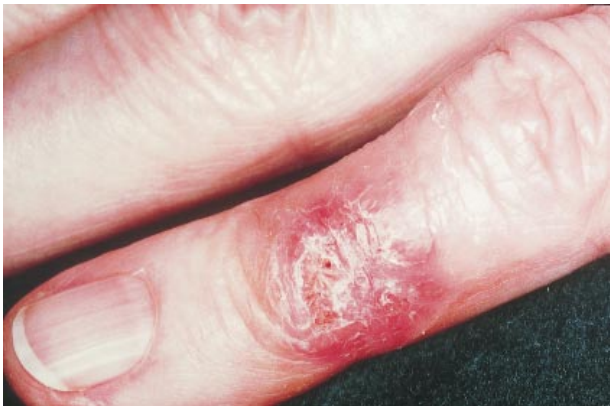

Figure 1. A scaly erythematous plaque is evident on the dorsal aspect of the little finger of the left hand.

In close co-operation with the responsible heart transplantation centre, therapy with itraconazole 400 mg daily was commenced. The serum level of tacrolimus was measured regularly because of the known pharmacological interaction between itraconazole and tacrolimus. After 6 weeks of treatment the size of the skin lesions had reduced significantly. The itraconazole dosage was then reduced to 200 mg daily. The lesions resolved clinically following another 4 months of treatment.

Discussion

With respect to the pathogenesis of cutaneous alternarioses, two possible routes of infection are distinguished. In the exogenous variant, the condition results from traumatic inoculation of fungal elements (e.g. after injury by a plant spine) or develops after

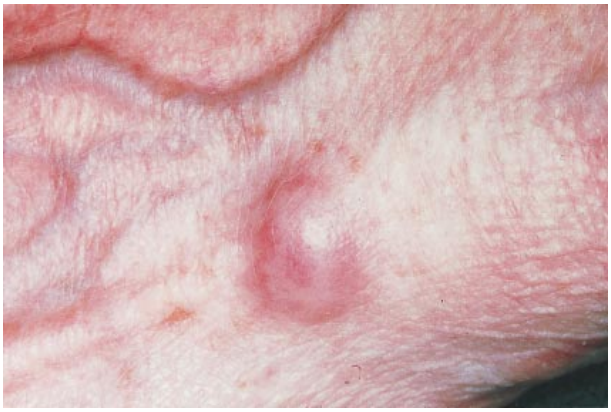

Figure 2. An erythematous nodule may be seen on the back of the left hand.

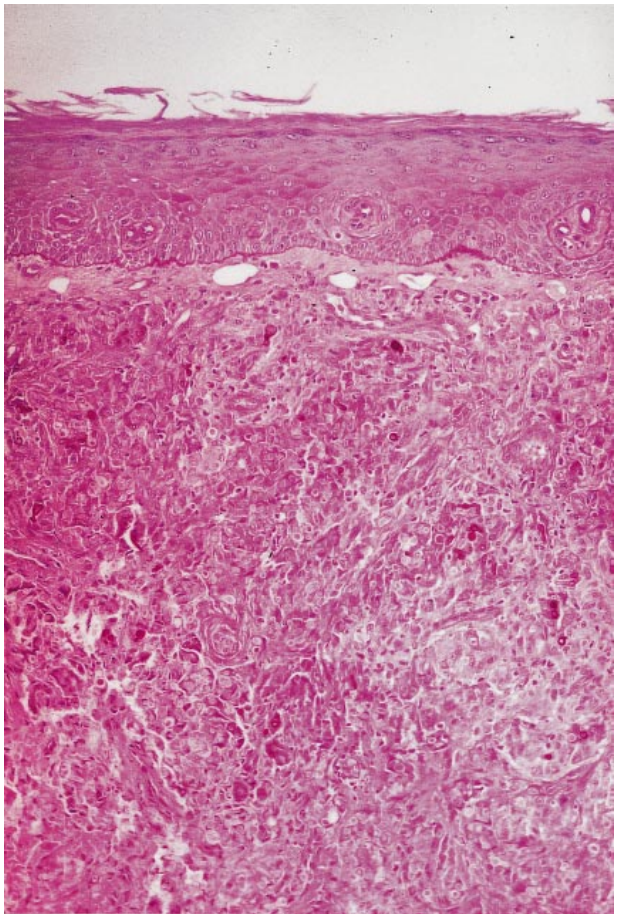

Figure 3. Histological examination of a biopsy from the back of the left hand shows fungal elements diffusely distributed in the dermis (periodic acid-Schiff stain, original magnification ×10).

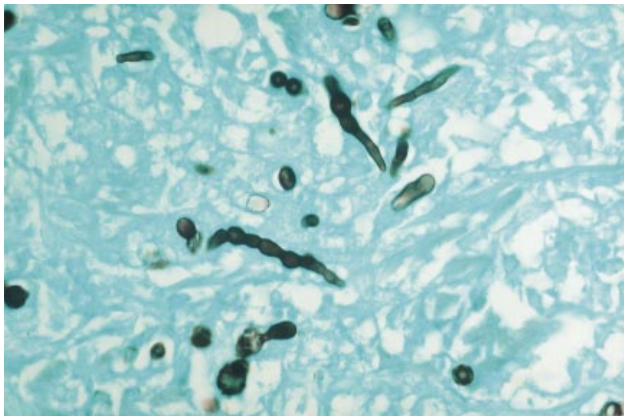

Figure 4. Histological examination of a biopsy from the back of the left hand shows budding cells and spheroidal chlamydospore-like structures (Grocott stain, original magnification ×40).

colonization of pathologically altered skin. In the endogenous variant, inhalation of fungal conidia and subsequent systemic spread eventually result in secondary cutaneous involvement.[2] An altered host resistance appears to be the prerequisite in the majority of affected patients; cutaneous alternarioses have been described in patients with Cushing's syndrome, lymphoproliferative disorders and AIDS, and following liver and kidney transplantation.[2,5–7] The spectrum of clinical presentations is broad. Verruciform and eczematous skin lesions, chronically vegetating tumorous infiltrates and multiple ulcerating lesions have been documented in the literature.[2,7]

The histological picture of cutaneous alternariosis is characterized by a granulomatous infiltrate with histiocytic giant cells, and the presence of spheroidal chlamydospore-like structures and gnarled, thick-walled, septate elements.[2,6] In some cases pigmented hyphal elements may become detectable with melanin staining (Fontana–Masson), thus leading towards the diagnosis of phaeohyphomycosis.[8] For further identification, mycological culture is required.

Species of the genus *Alternaria* show rapid colony growth, with colonies that have a grey to olivaceous-black undersurface on Sabouraud's dextrose agar. In fully developed colonies of *A. infectoria*, microscopic examination reveals non-branched, irregularly interrupted, dark conidiophores up to 80 μm long and 3–6 μm in diameter.[1] The mostly ovoidal conidia are arranged in branched chains and have long apical beaks. The latter develop into deep brown, secondary conidiophores. In contrast to the common saprobe *A. alternata*, *A. infectoria* produces whitish colonies on dichloran rose Bengal yeast extract sucrose agar.[1] In the literature *A. alternata* has commonly been considered as the causative organism of cutaneous alternariosis.[2,5,7,8]

Successful treatment of cutaneous alternariosis with itraconazole has been reported previously.[5,8] Attention must be paid to possible interactions with other concurrent medications. Given the underlying immunosuppression of the patients, long-term therapy over a period of at least 6 months appears advisable.

The case presented here appears remarkable for the sporotrichoid distribution of the skin lesions. Such a distribution is mainly seen in sporotrichosis caused by *Sporothrix schenckii*, but has also been described in mycobacterial infections and leishmaniasis.[9] To our knowledge, this clinical picture has not been documented with cutaneous alternariosis before.

In this case, identification of the causative organism *A. infectoria* was achieved by sequencing of the rDNA ITS region and comparison with over 100 ITS sequences taken from the public domain and generated from strains maintained in the CBS reference collection.[9] Full identity was observed with the type strain of *A. infectoria*, while *A. alternata* was significantly different, e.g. by the absence of a 26-bp Indel in ITS1.

Resistance of dematiaceous fungi to various antimycotic drugs has been described in the literature.[10] Because successful treatment of cutaneous alternariosis with itraconazole has been reported,[5,8,10] this drug appears to be the first-line treatment in this condition, especially in recognition of its low toxicity.

The case presented here indicates a potentially important role of molecular biological examination in cutaneous mycotic infections in the future.

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