Emerging Cutaneous Phaeohyphomycosis Caused by 
Alternaria infectoria

Feohifomicose Cutânea Emergente Causada por Alternaria infectoria

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ABSTRACT

Alternaria species belong to a group of opportunistic fungi that causes skin infection mainly in immunosuppressed patients. The authors describe two clinically distinct cases of cutaneous alternariosis caused by Alternaria infectoria in patients under prolonged corticosteroid treatment. Additionally, a brief review of published cases in portuguese patients is conducted.

Keywords: Alternaria; Dermatomicose; Immunocompromised Host; Phaeohyphomycosis

RESUMO

As espécies Alternaria pertencem a um grupo de fungos oportunistas que causam infeções cutâneas, nomeadamente, em doentes imunocomprometidos. Os autores descrevem dois casos clínicos distintos de alternariose cutânea causada por Alternaria infectoria em doentes sob corticoterapia prolongada. Adicionalmente, é também feita uma breve revisão dos casos publicados em doentes portugueses.

Palavras-chave: Alternaria; Dermatomycoses; Feohifomicose; Hospedeiro Imunocomprometido

INTRODUCTION

Phaeohyphomycosis refers to a chronic infectious condition caused by a heterogeneous group of fungal pathogens, known as dematiaceous fungi, characterized by the formation of dark colonies in culture, due to the production of a melanin-like pigment. Alternaria, a saprophytic fungus, present in soil, air and on plants, is one of the most frequent causative agent of cutaneous phaeohyphomycosis representing an important emerging pathogen in immunocompromised patients.1 Most of the cases of cutaneous alternariosis reported in the literature refer to solid organ transplant recipients, with hypercortisolism being an important risk factor for this infection.2,3

Clinical manifestations are frequently deceptive, ranging from an insignificant lesion to multiple inoculation sites.2,4 Even though there are no guidelines for the treatment of cutaneous alternariosis, surgical excision alone or in combination with systemic antifungal treatment results in cure of the infection in most cases.5 In this report we describe two clinically different cases of cutaneous alternariosis: one patient chronically treated with corticosteroids and azathioprine and another patient treated solely with prolonged corticosteroid therapy. In the end, a brief review of published cases in Portuguese patients is carried out.

CASE REPORTS

Case 1

A 61-year-old woman was observed in the Dermatology department for slowly growing asymptomatic cutaneous lesions on her extremities over the previous year. Physical examination revealed firm and well-defined erythematous-violaceous nodules covered with central hematic crust located on the right forearm in a sporotrichoid distribution (Fig. 1) and solitary nodules on the left elbow and right ankle. The patient resided in rural area and reported occasional gardening, but denied history of preceding local trauma.

The patient’s previous medical history included myasthenia gravis diagnosed two years before and treated with pyridostigmine 240 mg/day, prednisolone 20 mg/day, and azathioprine 100 mg/day.

Given the clinical picture presented, deep fungal or mycobacterial infection was suspected. Diagnostic tests, including blood and urine cultures, HIV, HBV, HCV serologies, chest x-ray, and abdominal ultrasound did not show any evidence of other foci of disease.

We performed two skin biopsies for histopathological examination and for culture. Histological sections of the biopsy specimen showed epidermal hyperplasia, dermal polymorphic infiltrate with histiocytes and granuloma formation. Periodic acid-Schiff (PAS) and Grocott stains showed hyphae and oval spore-like structures (Fig. 2). Cultures of cutaneous biopsy grew Alternaria sp., later identified by polymerase chain reaction (PCR) as Alternaria infectoria.

The patient initiated itraconazole 200 mg/day along with corticosteroid tapering, and continued azathioprine 100 mg/day with controlled myasthenic symptoms. Two large nodules were concomitantly treated with cryosurgery. After six months of...
oral anti-fungal treatment, the lesions were completely healed, and no relapses were observed during a two-year follow-up.

Case 2

A 79-year-old woman, with medical history of endometrial adenocarcinoma in remission (having underwent surgery and radiotherapy four years before) and degenerative axial changes, treated with methylprednisolone 16 mg/day for more than one year and buprenorphine 35 mcg/hour transdermal patch, presented to an urgent dermatology consultation with an asymptomatic but slowly progressing plaque on the lateral aspect of the right leg (Fig. 3A). Clinical observation of the lesion revealed small erythematous-brown papules and nodules with spontaneous haemato-purulent exudation. Dermatoscopy of the inflammatory papules unveiled dark brown to grey pigment surrounded by irregularly shaped red patches with blurred borders (Fig. 3B).

Skin biopsy was performed along with the collection of purulent material for microbiological examination. The histopathologic examination showed sepatate hyphae in a granulomatous dermal infiltrate. Mycological culture isolated a dematiaceous fungus, Alternaria species. The Alternaria infectoria diagnosis was made by PCR.

The patient initiated itraconazole 200 mg/day and the analgesic therapy was adjusted in order to slowly decrease the dose of methylprednisolone. After six months of treatment, complete recovery was observed, leaving residual postinflammatory hyperpigmentation (Fig. 3C), with no relapses.

DISCUSSION

Alternaria is a very common, ubiquitous fungus with a worldwide distribution, linked to hypersensitivity reactions mainly in asthma patients and to several human infectious diseases, e.g. paranasal sinuses, ocular, cutaneous and subcutaneous infections in immunocompromised patients. Interestingly, most of the cases of cutaneous alternariosis are being reported from Europe, mainly from Mediterranean countries.6

In Portugal, to date, 17 cases were reported, in addition to two cases presented in this report (Table 1). In our review, 12 males and seven females were included, with ages ranging from 43 to 79 years old. According to the review, 84% of cases (16/19) were solid organ transplant recipients on multiple immunosuppressive agents including glucocorticoids, tacrolimus, azathioprine, cyclosporine and mycophenolate mofetil. The altered cell-mediated immunity and reduction of intraepithelial antigen-presenting Langerhans cells significantly contribute to increased risk of opportunistic fungal infections in these patients.6 Two cases were non-recipient transplant patients and were linked solely to chronic corticosteroid treatment. In addition to immunosuppression induced by glucocorticoids, cutaneous atrophy and fragility caused by this treatment represent an important cofactor permitting direct inoculation from the environment.7

The clinical picture is non-specific and varies from patient to patient, as shown in the presented cases. The lesions generally appear on exposed areas of the extremities as solitary or grouped papules or papule-nodules that evolve into ulcers and erythematous infiltrating patches.2,4 Dermatoscopy of the lesions reflects the presence of melanin in the fungal wall and may serve as an useful tool to identify dematiaceous fungi and distinguish them from other infectious agents.

Alternaria is present in the environment and frequently occurs as a laboratory contaminant. Therefore, the diagnosis must be based on isolation in culture and concomitant demonstration of fungal structures in tissues. More recently, the use of molecular techniques has facilitated the identification of different Alternaria spp.3,7,8 In the Portuguese series of patients, Alternaria alternata was the most frequent causative agent (52%), followed by Alternaria infectoria (42%), including one case of mixed infection.3 Alternaria chartarum was diagnosed only in one patient.10

Treatment of cutaneous alternariosis remains non-standardized since no clinical trials have been performed to date. If possible, reduction of immunosuppression is indicated and can be effective in the treatment.11 Among systemic antifungal drugs, itraconazole is the most commonly used treatment. In our review, itraconazole was used in 80% of patients, either alone or in combination with surgical techniques, such as conventional excision or cryosurgery. Other treatment options include amphotericin B, voriconazole or posaconazole.5,7,8,12

The present work underlines the importance of recognizing this rare condition, knowing that the infection may be frequently underdiagnosed, as the appearance of lesions non-specific and may resolve after reduction or cessation of immunosuppressive treatment. Infections by phaeohyphomycoses should be considered in the differential diagnosis of all chronic skin lesions in patients who have underwent organ transplant or patients with other conditions which require prolonged corticosteroid or another immunosuppressive treatment.

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PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association published in 2013.
DATA CONFIDENTIALITY
The authors declare having followed the protocols in use at their working center regarding patients’ data publication.

PATIENT CONSENT
Obtained.

CONFLICTS OF INTEREST
The authors declare that there are no conflicts of interest.

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REFERENCES

Figure 1 – *Alternaria infectoria* skin infection. Erythematous nodules in a sporotrichoid distribution on the dorsal aspect of the right forearm.
Figure 2 – Histopathology examination using Grocott methenamine silver stain highlights fungal hyphae and oval spore-like structures.

Figure 3 – Cutaneous Alternaria infectoria infection. (A) Plaque consisting of multiple erythematous brown papules and nodules on the lateral aspect of the right leg. (B) Dermatoscopy (10x magnification) reveals dark brown to gray pigment surrounded by irregularly shaped red patches with blurred borders. (C) Residual post-inflammatory hyperpigmentation after 6 months of treatment.
<table>
<thead>
<tr>
<th>Age</th>
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<th>Associated condition</th>
<th>Initial immunosuppressive regimen</th>
<th>Alternaria spp.</th>
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CT: corticosteroid treatment; Pred: prednisone; Tacr: tacrolimus; Aza: azathioprine; MFM: mycophenolate mofetil; CyA: cyclosporine A.