Subcutaneous Phaeohyphomycosis caused by *Veronaea bothryosa*: report of 2 cases*

*Feo-hifomicose causada por Veronaea bothryosa: relato de dois casos**

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Abstract: Phaeohyphomycosis caused by *Veronaea bothryosa* is very rare. We report two cases. To our knowledge, these are the first and second cases to be reported on the American continent, and fourth and fifth cases in the world literature. We report one case in a kidney transplant recipient, and another case in an immunosuppressed non-transplant patient. Both patients presented with a lesion on the dorsal aspect of the foot, following trauma. One patient responded moderately well to treatment with itraconazole. The other responded well to a surgical excision.
Keywords: Surgery; Dermatomycoses; Mitosporic fungi; Immunosuppression; Opportunistic infections; Itraconazole; Male; Mycoses; Kidney transplantation.

***Resumo**: Feo-hifomicose causada por Veronaea bothryosa é muito rara. Os autores relatam dois casos, que acreditam ser o primeiro e o segundo no continente americano, mas quarto e quinto da literatura mundial, até o momento. Trata-se de dois pacientes, um transplantado renal e outro imunossuprimido não transplantado. Ambos apresentavam lesões no dorso do pé após trauma. O primeiro respondeu moderadamente ao tratamento com itraconazol, e o segundo respondeu muito bem à excisão cirúrgica.*
Palavras-chave: Cirurgia; Dermatomicoses; Fungos mitospóricos; Imunossupressão; Infecções oportunistas; Itraconazol; Masculino; Micoses; Transplante de rim.

INTRODUCTION

Phaeohyphomycosis is a disease caused by dematiaceous fungi characterized by hyphae and pigmented fungal cells in the infected tissue. These fungi live like saprophytes in soil, vegetation and water.[1,2] The group's main clinical importance is due to a growing incidence and severity of the infection, which may lead to death. Immunosuppression of diverse causes seems to have a strong influence on the problem's pathophysiology. Dermatology has a fundamental role to play, given that one of the most affected sites is the skin.

Two cases of phaeohyphomycosis caused by *Veronaea bothryosa* are reported in this study. They were both immunosuppressed under different conditions. The former occurred in a renal transplant recipient utilizing immunosuppressor drugs. The latter patient had a chronic obstructive lung disease and was under non controlled corticotherapy.

CASE REPORT

Case 1

A 44-year-old white male patient from Arroio do Sal, a coastal town in Rio Grande do Sul state, had a kidney transplant carried out five years ago. He was treated with immunosuppressor drugs (cyclosporine,

Received on May 08,2003.
Approved by the Consultive Council and accepted for publication on November 01,2004.
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azathioprine and prednisone). The patient reported a trauma on the left foot from a wooden splinter, which occurred three years prior to the consultation, although the lesion developed only three months ago. The patient also referred to an attempt at removing the lesions, as he believed it to be a wart.

The dermatological examination revealed a lesion that was painful to touch. It had an erythematous-violet color and a tumoral aspect with a central cavity and slight exudation (Figure 1). The anatomic and morphologic examination showed chronic dermatitis with structures pigmented by hematoxylin-eosin. Grocott-Gomori methenamine staining demonstrated that there were fungal elements (Figure 2). The direct (KOH) examination revealed dematiaceous hyphae (Figure 3). The urease test was positive. In the Sabouraud dextrose agar culture, there was quick growth of the raised colony, which went from grey to black, was velvety and characteristic of the dematiaceous filamentous fungus (Figure 4). The microscopy was typical of *Veronaea bothryosa* (Figure 5).

Therapy was begun with terbinafine 250 mg daily for 28 days. There was no response during this period, and new lesions emerged in the pretibial homolateral region, which suggests increasing dissemination along the path of the lymphatic vessels (Figure 1). New therapies were introduced with itraconazole 200 mg daily. There was then a significant reduction of pain, lesion size and exudation in the 25 and 40-day follow-up sessions. On the other hand, new lesion material collection resulted in positive direct mycological examinations and cultures. The new approach involved tapering the dose of the immunosuppressor drugs as suggested by the hospital transplant center. Itraconazole was kept at the same doses for roughly 10 months. In spite of there not being a reduction of lesions with this new approach, there was no complete clinically remission. The disease activity was confirmed by positive mycologic examinations. The patient died at the end of this period due to complications arising from an accidental cerebral vascular hemorrhage. The serology for HIV I and II was negative. The fasting glycemia, hematocrit, hemoglobin and leukocytes were normal.

Case 2

A white 64-year-old patient from the mountainous region of Rio Grande do Sul state, presented with an asymptomatic lesion on the dorsal aspect of the right foot, resulting from a trauma from a corn husk. Two years ago, the patient utilized 40 mg of prednisone daily with the objective of alleviating chronic obstructive pulmonary disease (COPD), without clinical follow up. The physical examination revealed cushingoid facies and edema of the lower limbs. The dermatological examination identified a small erythematous-violet papule (Figure 6).

Direct examination of the lesion (KOH) showed dematiaceous hyphae. There was rapid growth of dark-grey colonization, with a velvety surface in the middle of the culture as well as a dematiaceous filamentous fungus (Figure 4). The microscopy was characteristic of *Veronaea bothryosa* (Figure 5).

The anatomopathologic examination revealed dermatitis with spongiosis foci and dematiaceous fungal structures. A large excision was performed. There was no recurrence up to the present moment (with 13 months of follow up). The patient was referred to the Pneumology Sector in order to manage his lung disease adequately. The serology for HIV I and II was negative. The fasting glycemia, hematocrit, hemoglobin and leukocyte count was normal. The chest X-ray showed significant COPD.

DISCUSSION

The agents responsible for phaeohyphomycosis include a large number of genera and different species. In accordance with the literature, *Exophiala* and *Alternaria* are possibly the most relevant of the opportunist pathogens.[1-4] Infection by V*eronaea bothryosa* is extremely rare. There have been merely three cases reported in the international literature, oddly in countries as distant from one another as China, Libya and France. The first case of phaeohyphomycosis caused by this fungus was reported by Nishimura, in China, but does not feature patient data or disease presentation.[5] The second case described in the literature refers to an apparently healthy woman from Libya, who presented with cutaneous lesions and oral ulcers (letter from Ayadi, The Lancet, 1995). The latest case described involves a hepatic transplant recipient in France, from

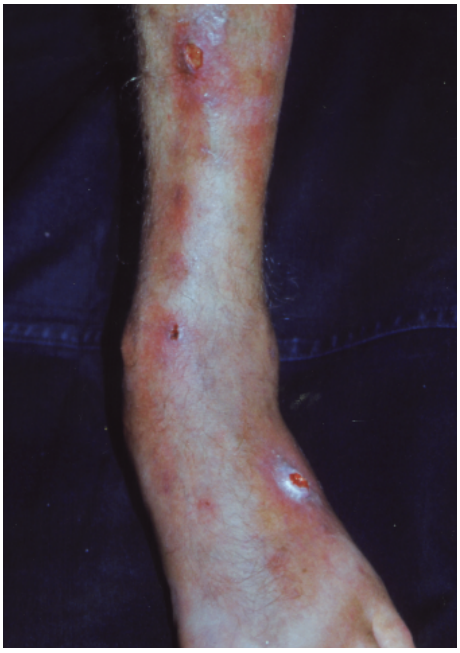

Figure 1: Case 1 - Erythematous-violet papule on the dorsal aspect of the foot and new lesions while using terbinafine.

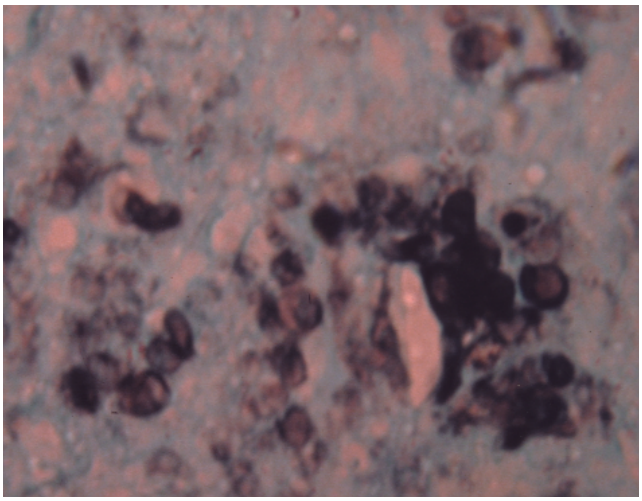

Figure 2: Case 1 - Fungal structures: hyphae and round forms - detail in the right corner (Grotto methenamine-black X120)

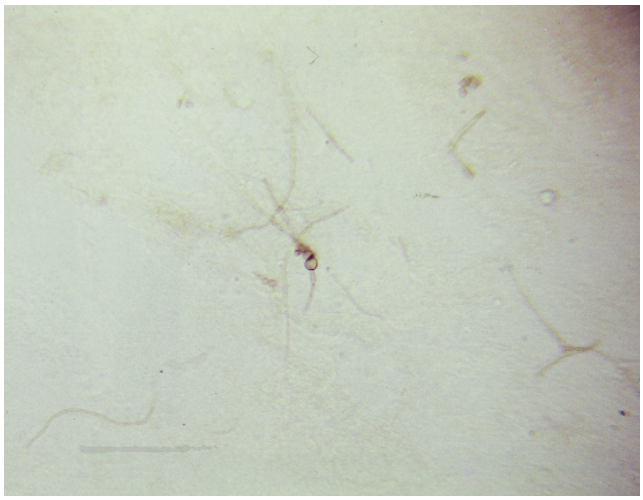

Figure 3: Case 1 - Dematiaceous Hyphae in the direct mycologic

1996.[6] Recently, Polish researchers found this fungus in the water and snow in coniferous trees.[7]

The present report is the first of its kind on the American continent. In it, we consider two patients, the fourth and fifth cases described in the international literature on phaeohyphomycosis caused by *Veronaea botbryosa*. One of the patients was a kidney transplant recipient, while the other patient was non-transplant immunocompromised.

The real prevalence of phaeohyphomycosis is not known. Apparently it is most frequent in immunosuppressed patients. Patients submitted to corticotherapy,[8] iatrogenic Cushing's syndrome and *diabetes mellitus*,[9] transplants treated with immunosuppressor drugs,[6] patients with severe diseases (tuberculosis in elderly patients),[3] with pemphigus and corticoid-induced diabetes,[10] in chemotherapy due to malignant diseases of the lymphohematopoietic system,[11] premature infants,[12] and in infants receiving intralesional (intra-articular) corticotherapy at the lesion site.[4] Meanwhile, cases do exist in clinically healthy persons who are not under medication.[13]

A diagnosis of phaeohyphomycosis is based on the mycological examination, given that the clinical presentation might be variable and the anatomopathological examination might be non-specific. In spite of this, histopathology might help to identify inflammatory alterations and dematiaceous fungal elements, thereby indicating a deep mycosis caused by a pigment-producing fungus. The round forms might be seen either in chromoblastomycosis or in the phaeohyphomycosis caused by opportunist pathogens. This is why the direct mycologic examination and culture microscopy are necessary for the diagnosis of the etiologic agent, especially in verrucous lesions. In the phaeohyphomycosis, direct mycologic examination allows dematiaceous hyphae to be visual observed, which is not possible in chromoblastomycosis, which only identifies round bodies.[1,2]

The culture microscopy was quite characteristic in

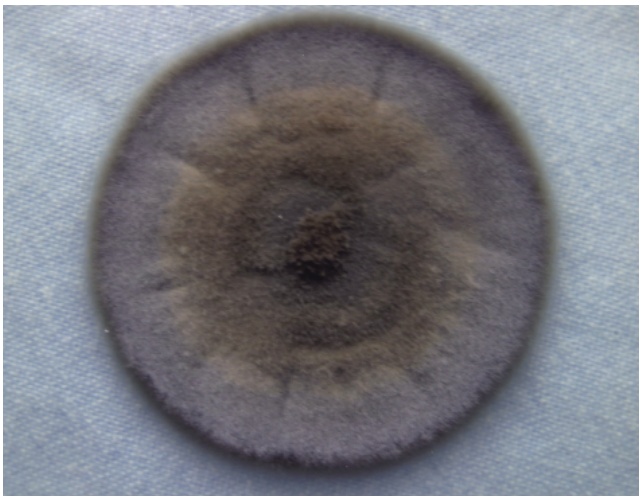

Figure 4: Case 1 - Growth of *Veronaea botbryosa* (Sabouraud agar)

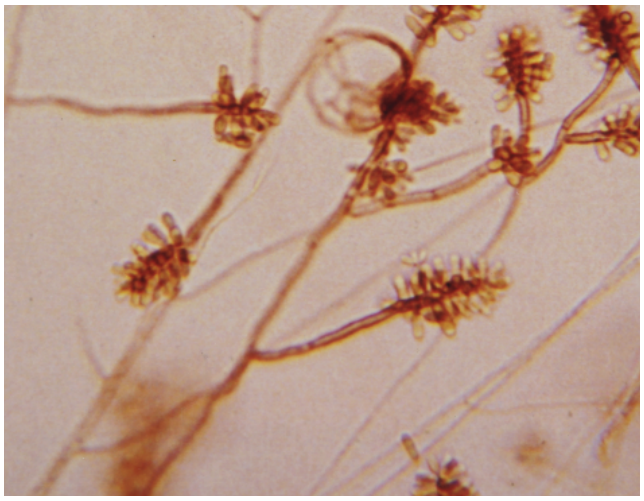

Figure 5: Case 1- Microscopy typical of *Veronaea botbryosa*

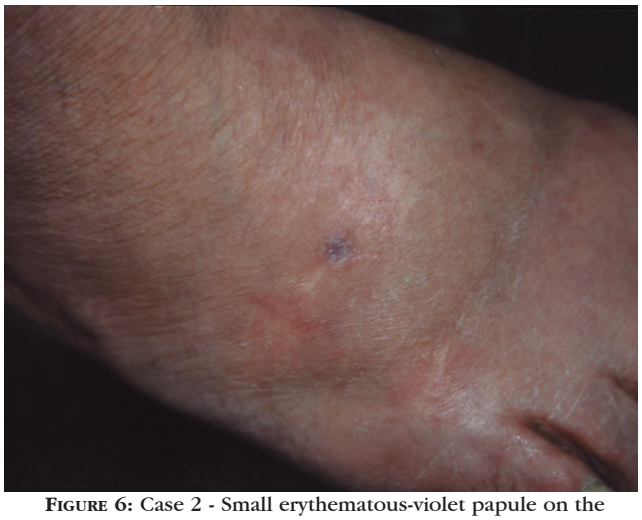

Figure 6: Case 2 - Small erythematous-violet papule on the dorsal aspect of the foot.

both cases. It allowed a definitive diagnosis of infection by *Veronaea bothryosa* to be established. This is a dematiaceous fungus with erect conidiophores. It is seldom ramified and has smooth walls. The conids present as cylindrical, varying from 5-to-12 per 3-to-4 micra with round apexes. They virtually always have a septum (Figure 5). This set of morphological findings is distinct of the species.[1,2]

A background of trauma is not always present in cases of phaeohyphomycosis. There is some debate as to whether the fungi are latent in the host or whether there is lesion development only with reduced immunity. The disease course is frequently slow in immunocompetent patients. On the other hand, dissemination occurs not infrequently by the internal organs, while recurrence does occur in immunocompromised patients.

Currently there is no standard treatment for this type of infection. In turn, it poses a great therapeutic challenge. The best option is for empirical treatment by observing prior reports. Therefore, any previously utilized treatments will have to have their effectiveness studied. The present authors would like to recall that terbinafine was not effective in its first case. There was moderate response to itraconazole 200 mg daily (namely, there was a clinical reduction, but without total remission of the lesions and the mycological culture remained positive). Terbinafine has been utilized,[14] but the drug to be most employed remains itraconazole in doses of 200 and 400 mg daily.[4,13,15] A description does exist of amphotericin by itraconazole.[11] Excision is an accepted method, whether in association with antifungal drugs or not.[4,8,15]

Further studies must be prompted so as to obtain more reliable epidemiologic data and more effective therapy despite all the difficulties involved in treating rare diseases. Physicians must be alert to the first signs of this type of infection, given that the transplant recipient and immunosuppressed population have significantly increased in size. Prompt diagnosis and treatment might reduce morbidity, as well as increase the probabilities of a cure and better control of the disease. ❑

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