

Phaeohyphomycosis in renal transplantation: report of two cases*

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Abstract: Phaeohyphomycosis is an infection caused by a filamentous fungus that contains pigment melanin in its cell wall. We report two cases caused by *Exophiala* sp. emphasizing the clinical variability of the disease, as well as diagnostic and therapeutic difficulties of this opportunistic infection in immunosuppressed patients (kidney transplant).

Keywords: *Exophiala*; Immunosuppressive agents; Kidney transplantation; Phaeohyphomycosis

INTRODUCTION

Phaeohyphomycosis is a rare opportunistic infection caused by a heterogeneous group of pigmented filamentous fungi.^{1,2} These fungi are saprophytic in nature but may be highly pathogenic in immunocompromised individuals. In these patients, clinic manifestations may be quite varied.¹ The disseminated form of the disease is associated with severe clinical presentation and mortality rates of up to 70%. We present two cases of phaeohyphomycosis in kidney transplant patients. We demonstrate the diagnostic and therapeutic difficulties of this opportunistic infection that may present a high risk of dissemination and high mortality rates in these patients.

CASE REPORT

CASE 1

A 57-year-old male patient presented for 2 years multiple nodules and tumors of cystic consistence on the back of right foot and right leg (Figure 1). The lesions exhibited a sporotrichosis-like distribution pattern but there was no history of local trauma. The patient received a kidney transplant 4 years ago due to

hypertensive nephropathy and his immunosuppressive treatment included azathioprine, tacrolimus and prednisone. The initial diagnostic hypotheses were sporotrichosis, paracoccidioidomycosis, leishmaniasis and phaeohyphomycosis. Direct mycological examination revealed irregular and septate moniliform hyphae of pigmented fungi. Culture on Sabouraud-Agar with chloramphenicol demonstrated vegetative chambered hyphae with septate annellophores, compatible with *Exophiala* sp. At the histopathological test a granulomatous inflammatory infiltrate was observed, in the form of brownish walls composed of giant multinucleated cells with fungal structures (Figure 2). Specific staining demonstrated pheomelanin in the fungi walls (Fontana-Masson) and search for fungi was positive (Gridley) (Figure 3). The patient was treated first with voriconazole 200mg 12/12h associated with surgical excision of lesions. During treatment with voriconazole the patient developed a severe clinical picture of hyponatremia; the drug was replaced with itraconazole 200mg/day, which was used during five months, with no relapses since then.

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FIGURE 1:
Nodules and tumors of cystic consistence on the right leg of a patient

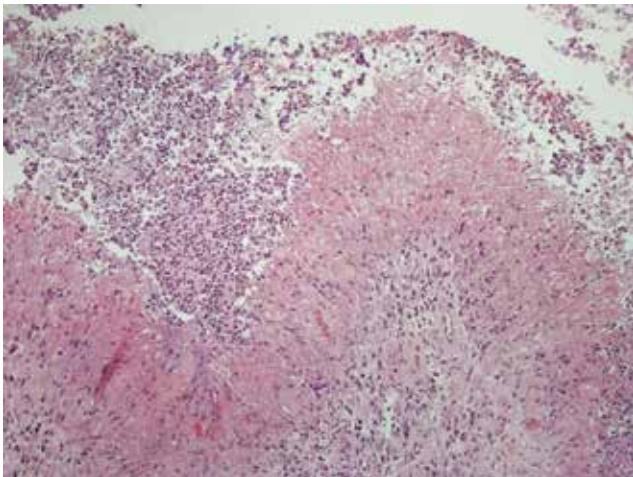


FIGURE 2: Inflammatory granulomatous infiltrate composed of giant multinucleated cells (HE x100)

CASE 2

A 59-year-old male patient presented for 8 months an erythematous-violaceous plaque covered with pustules and honey-colored scabs on the right thigh (Figure 4). No history of previous local trauma. The patient received a kidney transplant two years ago for hypertensive and diabetic nephropathy and the immunosuppressive treatment included mycophenolate sodium, tacrolimus and prednisone. The initial diagnostic hypotheses were squamous cell carcinoma, chromomycosis and phaeohyphomycosis. Direct mycological examination revealed irregular pigmented

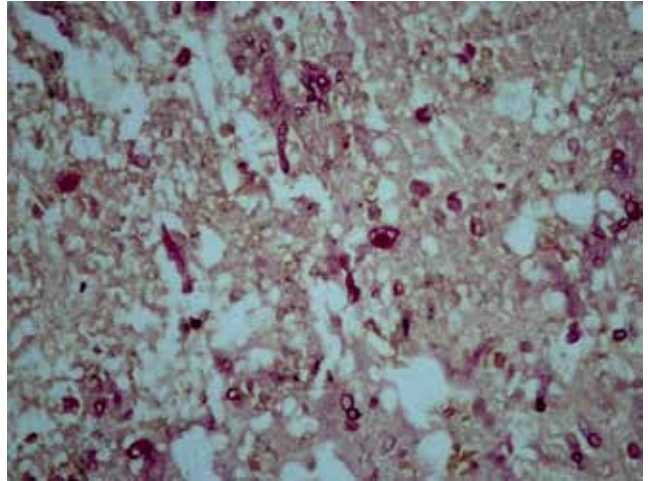


FIGURE 3: Positive search for fungi (Gridley x400)



FIGURE 4 : Erythematous-violaceous plaque, covered with pustules and honey-colored scabs on the right thigh of patient 2

and septate hyphae. The morphological aspect of culture on Sabouraud-Agar with chloramphenicol was compatible with *Exophiala sp.* At the anatomopathologic examination with specific staining were observed septate hyphae with acute angle ramification (Figure 5). The established treatment was surgical lesion excision associated with itraconazole 200mg/day during four months. Up to this time no signs of relapse have been observed.

DISCUSSION

Phaeohyphomycosis is an opportunistic fungal disease that predominantly affects the skin and may disseminate in immunocompromised patients. The incidence in transplanted patients is approximately 9%, with most cases occurring after the two first years following transplant, as observed in our patients.² This incidence has been increasing in the last decades due to the escalation in the number of transplant patients and the use of highly immunosuppressive drugs.

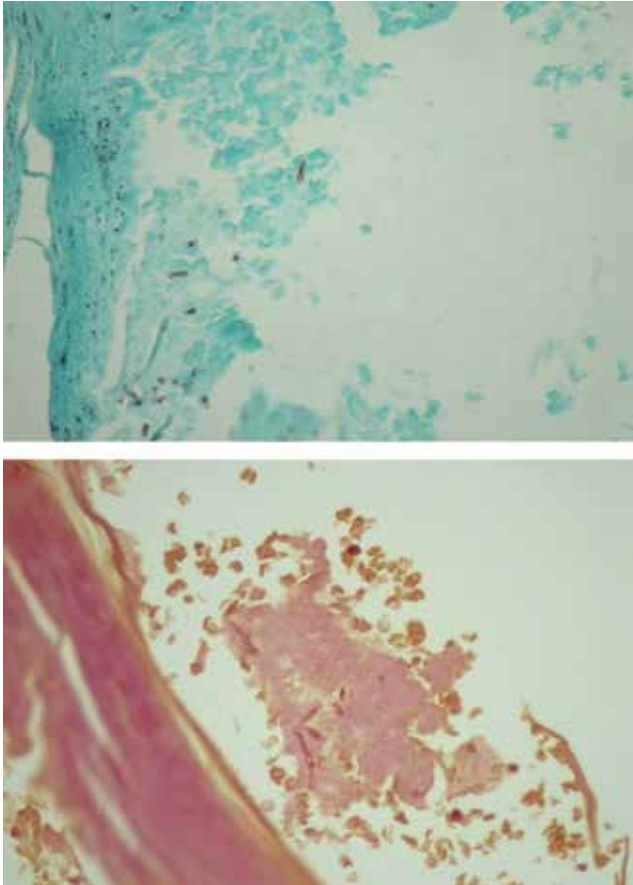


FIGURE 5 : Septate hyphae with ramification at an acute angle (Fontana-Masson x400; Gridley x400)

Although the new immunosuppressive drugs have improved survival rate of these patients, they are also associated with the increased morbidity and mortality due to opportunistic infections. Calcineurin inhibitors seem to increase susceptibility to fungal infections even more, when compared to other immunosuppressants.^{4,5}

The diagnosis becomes more difficult because of clinical polymorphism of lesions and the lack of serological or antigenic tests that may prove there is infection in the blood or tissues. The diagnosis of our patients was based on the clinical lesions and on direct mycological examination, on culture and anatomopathological examination, which are the main diagnostic tools.⁶ⁿ

In transplanted patients, the clinical polymorphism usually present in phaeohyphomycosis is exacerbated by the intense iatrogenic immunosuppression used, making diagnosis extremely difficult. They may present papules, nodules, erythematous plaques, abscesses, ulcers and/or tumors, which have in common the frequent involvement of subcutaneous tissue.

Up to this time there are more than 100 species of melanotic fungi associated with phaeohyphomycosis. *Alternaria sp*, *Curvularia sp* and *Exophiala sp* are the species most frequently found in transplanted patients.³

The fungus identified in our patients was *Exophiala sp.*, which is the most common etiologic agent in subcutaneous phaeohyphomycosis.^{7,8} There is no correlation established until now between etiologic agents and the clinical presentation of phaeohyphomycosis. Despite having the same etiologic agent, we observe a distinct clinical picture in our patients, a fact that may be justified by the different moment in the progression of the disease and the differences in the immunosuppressive scheme employed.

The treatment of phaeohyphomycosis is difficult and non standardized due to the rarity of the disease. In transplanted patients the therapeutic approach is challenging, as larger doses of antifungals are required and there is the possibility of drug interactions that may place at risk the functionality of the transplanted organ.

Surgical excision is the therapy of choice for localized and well-delimited lesions caused by *Exophiala sp*. The use of antifungal drugs is recommended for transplanted patients before and after surgery, but there is no consensus about the drug of choice nor length of treatment. In severe and/or disseminated cases it is also recommended to reduce the immunosuppressive doses.^{6,9}

Most of the melanotic fungi are susceptible to azolics, making itraconazole and voriconazole the main drugs employed, followed by amphotericin B.²

In transplanted patients, the high doses of azolics may trigger drug interaction with calcineurin inhibitors and MTOR as they are important CYP3A4/5 inhibitors.¹⁰ This interaction may raise the serum levels of immunosuppressants to extremely toxic levels. On the other hand, reduction of immunosuppressant doses to extremely low levels may trigger functional loss of the transplanted organ.

The early clinical suspicion of phaeohyphomycosis in transplanted patients becomes extremely important, since immunosuppression is the main risk factor for infection and responsible for systemic dissemination of the disease, culminating in severe and fatal clinical pictures.

Therefore, the importance of this article resides in the fact that it demonstrates two distinct clinical forms of phaeohyphomycosis in kidney transplant patients (disease with increased incidence in this population of patients) and for pointing out the diagnostic and therapeutic difficulties, as well as the possibility of drug interaction. □

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