

Subcutaneous Phaeohyphomycosis in a Patient with Metabolic Comorbidities: A Rare Diagnostic Alert in a Low-Resource Setting

Inggyrd Eduarda Possidônio de Souza Santos ^{1,*}, Guilherme Alencar de Medeiros ², Patrícia Cristina Ribeiro Conceição ², Daniel Wagner de Castro Lima Santos ^{3,4}, Conceição de Maria Pedrozo e Silva de Azevedo ¹

¹ Federal University of Maranhão (UFMA), São Luís, Maranhão, Brazil.

² Cedro Laboratory, São Luís, Maranhão, Brazil.

³ Presidente Dutra University Hospital (HU-UFMA), Federal University of Maranhão (UFMA), São Luís, Maranhão, Brazil.

⁴ Rede D'Or IDOR, Brazil, São Luís, Maranhão, Brazil.

* Correspondence: inggyrd734763@gmail.com.

Abstract: Phaeohyphomycosis is a rare subcutaneous fungal infection caused by melanized (dematiaceous) fungi, usually linked to trauma and, in some cases, to immunosuppression. We report the case of a farm worker living in a remote area of Maranhão, Brazil, with limited access to specialized health services. The patient had systemic arterial hypertension and insulin-dependent type 2 diabetes mellitus, metabolic comorbidities that may increase susceptibility and influence the course of infection. He developed multiple subcutaneous nodules and long-standing fistulized, draining masses on the right upper limb. The diagnostic pathway was prolonged, reflecting challenges in areas with limited health infrastructure, where general practitioners often have little training in endemic fungal diseases because they are perceived as uncommon in routine practice. An initial biopsy led to an incorrect diagnosis of chromoblastomycosis. The definitive diagnosis was established after referral to a specialized hospital, with magnetic resonance imaging (MRI) showing multiple nodular subcutaneous lesions, direct microscopy revealing septate dematiaceous hyphae, and fungal culture isolating *Exophiala* spp. Treatment with itraconazole at 400 mg/day led to progressive clinical improvement and a marked reduction in lesion size. This case highlights the importance of early clinical suspicion of subcutaneous phaeohyphomycosis, even in patients without classic immunosuppression, particularly when metabolic comorbidities are present.

Keywords: Phaeohyphomycosis; Immunocompetent patient; *Dematiaceous fungi*; Itraconazole.

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1. Introduction

Phaeohyphomycosis refers to infections caused by melanized (dematiaceous) fungi, which contain melanin in their cell wall and therefore appear darkly pigmented. Melanin acts as a virulence factor, helping fungi evade host immune responses and antifungal activity [1]. Infection is usually associated with immunosuppression or host frailty, although immunocompetent individuals may also be affected [2, 3]. *Dematiaceous fungi* are widespread in the environment, particularly in tropical and subtropical regions [2, 4]. They are found in soil and decaying wood, which increases exposure among individuals engaged in agricultural work [5]. Phaeohyphomycosis affects men more frequently [6]. Epidemiological studies suggest this predominance is related to occupational and behavioral factors, such as greater exposure to contaminated environments and a higher frequency of cutaneous trauma [7, 8].

Phaeohyphomycosis is often described in immunocompromised patients, especially organ transplant recipients, people living with HIV, and patients with hematological disorders [9]. However, cases have been reported in patients without immunosuppression. The first reported case in Latin America of subcutaneous phaeohyphomycosis caused by *Cladophialophora bantiana* occurred in an immunocompetent individual. The patient had a slowly progressive lower limb lesion and was successfully treated with surgical excision combined with antifungal therapy [3]. There are no national epidemiological data on the occurrence and magnitude of phaeohyphomycosis in Brazil because endemic mycoses are not included in the national list of notifiable diseases [5].

Phaeohyphomycosis is caused by dematiaceous fungi, which are characterized microscopically by dark colonies and septate hyphae and/or yeast-like elements with pigmented cell walls. Several genera can be involved, including *Wangiella*, *Alternaria*, and *Exophiala* [2]. The portal of entry is usually linked to the clinical presentation and may include traumatic inoculation, secondary contamination of pre-existing skin lesions, respiratory exposure to spores, and hematogenous dissemination, which is more closely related to systemic disease [2, 5]. Phaeohyphomycosis can be classified based on lesion location and route of inoculation. The most common form is cutaneous disease, affecting keratinized tissues and the dermis and presenting as a granuloma in subcutaneous fat due to traumatic implantation [5]. Lesions often involve the face or limbs because these areas are more exposed. Other forms include cerebral and disseminated disease, which may involve the central nervous system, skin, and other organs and are associated with higher mortality [2, 10, 11].

Diagnosis is based on direct microscopy and fungal culture, supported by the observation of brownish hyphae [2, 6, 12]. Histopathology can support diagnosis by showing inflammatory patterns ranging from granulomatous to pyogranulomatous. In some cases, diagnosis is made through biopsy of affected organs. Culture positivity and agent identification rates reach only about 50%, and species identification may not be possible based solely on colony morphology. In such scenarios, polymerase chain reaction (PCR) is an alternative, allowing faster and more sensitive identification [2, 13]. Additional exams may include cerebrospinal fluid analysis, antibody testing, computed tomography, and MRI [2].

Treatment depends on clinical form and host immune status. Antifungals such as itraconazole, voriconazole, and posaconazole have been used successfully for cutaneous and subcutaneous diseases. In severe or refractory infections, combining antifungal therapy with surgery may be necessary [14]. Although antifungal therapy plus surgery remains the most common strategy, management in immunosuppressed patients requires careful attention. In a retrospective study of 82 kidney transplant recipients diagnosed with phaeohyphomycosis or chromoblastomycosis, antifungal therapy combined with reduced immunosuppression was effective in most cases, although recurrences were reported [15]. Most authors consider itraconazole the first-line drug for phaeohyphomycosis [12].

Rapid identification of the etiologic agent enables appropriate antifungal selection and, when needed, surgical intervention. Preventive measures are also essential to reduce new cases [5]. The objective of this case report is to describe a case of subcutaneous phaeohyphomycosis caused by *Exophiala spp.* in a patient with metabolic comorbidities living in a low-resource setting, highlighting the diagnostic challenges, the risk of misdiagnosis with other subcutaneous mycoses, and the importance of early clinical suspicion and appropriate antifungal therapy for favorable outcomes.

2. Case Report

2.1 Case presentation

A 62-year-old man, a farm worker from rural Maranhão, Brazil, with a history of insulin-dependent type 2 diabetes mellitus and systemic arterial hypertension, presented

with an extensive lesion on the right upper limb. Symptoms began about one year earlier as a “lump” on the right arm that was surgically excised. Approximately two months after surgery, the lesion progressively spread throughout the right forearm, with multiple subcutaneous nodules and masses, some evolving with fistulization, serosanguinous-purulent drainage, and diffuse inflammation, without foul odor.

He sought medical care in his hometown. Fluconazole (450 mg/day) was prescribed, with no improvement after 30 days. A biopsy for histopathology was performed locally, and the diagnosis was reported as chromoblastomycosis, describing suppurative interstitial granulomatous dermatitis associated with pseudoepitheliomatous hyperplasia, intra-dermal abscess, and “sclerotic bodies”. Itraconazole (100 mg/day) started in September 2023, with no improvement, and he was referred to Hospital Presidente Vargas. The patient was admitted on May 28, 2024, with disseminated lesions and multiple nodules with serosanguinous-purulent drainage (Figure 1). On hospital day 1, a new biopsy was obtained for histopathology, direct microscopy, and fungal and bacterial cultures.

2.2 Direct microscopy

Direct microscopy material was collected on hospital day 1 and showed septate dematiaceous hyphae (Figure 2).

2.3 Fungal and bacterial cultures

Fungal culture was positive for *Exophiala* spp.

Figure 1. Right upper limb showing multiple lesions with subcutaneous nodules and masses, fistulization, and serosanguinous-purulent drainage on the first day of evaluation (D0).



2.4 Histopathology

Histopathology showed granulomatous dermatitis with fungal hyphae (Figure 3).

2.5 Magnetic resonance imaging (MRI)

MRI of the right forearm (hospital day 17) showed thickening of ventral, dorsal, medial, and lateral subcutaneous compartments with multiple nodular formations showing intermediate T1 signal and high T2 signal, with variable sizes up to 2.8×1.6 cm, causing local bulging and compressing superficial vascular structures (Figure 4).

Figure 2. Direct microscopy showing septate dematiaceous hyphae.



Figure 3. Histopathological examination shows granulomatous inflammatory infiltrate with fungal hyphae.

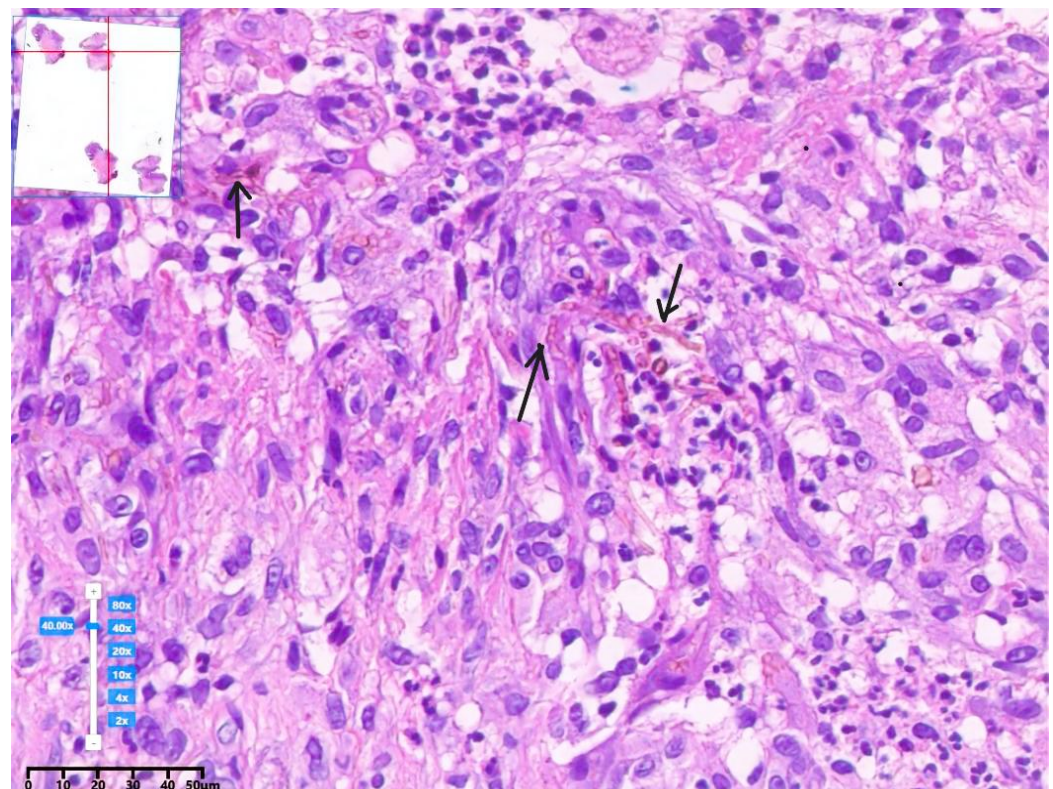
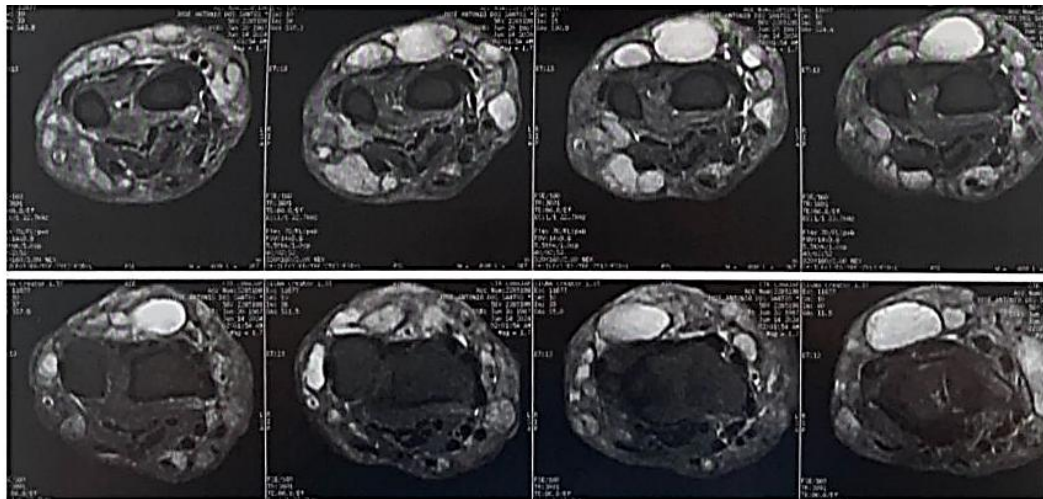


Figure 4. MRI showing multicompartiment subcutaneous and intermuscular nodular lesions with features suggestive of necrotic or liquefied content.



2.6 Clinical and therapeutic management

The patient was hospitalized on May 28, 2024 and started on piperacillin/tazobactam (4.5 g every 6 hours) and NPH insulin (10 IU-0-0-10 IU) due to poor glycemic control, and itraconazole 400 mg/day. He was discharged on hospital day 23 with itraconazole 400 mg/day (200 mg after main meals).

2.7 Follow-up

At outpatient follow-up 30 days after discharge, the patient had marked clinical improvement. Lesions were healing, without drainage or fistulas, with a significant reduction in limb inflammation, indicating effective itraconazole therapy. Strength and sensation were preserved (Figure 5). In addition to itraconazole, the patient was taking metformin 850 mg three times daily (1-1-1). He reported no other complaints. The plan was to maintain itraconazole 400 mg/day for an additional 60 days. The patient is currently followed every two months.

Figure 5. Clinical image of the right hand showing residual cystic nodules and scars from previous lesions, with minimal inflammation and no drainage.



3. Discussion and Conclusion

Phaeohyphomycosis is a subcutaneous fungal infection defined by the presence of melanized (dematiaceous) fungal elements in tissue and is more frequently reported in immunocompromised patients and organ transplant recipients [8, 16]. Typical cases, such as the report by Silva et al. [17] of subcutaneous phaeohyphomycosis caused by *Exophiala jeanselmei* in a heart transplant recipient, illustrate the severity and therapeutic challenges in immunosuppressed individuals, in whom itraconazole may be insufficient and more aggressive treatments such as amphotericin B may be required. Similarly, Fernandes et al. [18] described an immunosuppressed patient with phaeohyphomycosis due to *Cladophialophora sp.*, highlighting the indolent course and recurrence after surgical excision. This pattern may lead to confusion with benign lesions such as lipomas or epidermoid cysts, delaying definitive diagnosis [6, 18, 19].

In the present case, the key feature is the occurrence in a farm worker from a remote region of Maranhão with systemic arterial hypertension and insulin-dependent type 2 diabetes mellitus. Although these conditions do not represent classic immunosuppression (e.g., HIV infection, solid organ transplantation, or high-dose immunosuppressive therapy), diabetes and hypertension are metabolic comorbidities that may increase susceptibility to infection and contribute to chronicity and severity [20, 21]. Diabetes is associated with impaired neutrophil chemotaxis and phagocytosis and altered cell-mediated immunity, which can predispose patients to cutaneous and subcutaneous fungal infections [20].

Diagnosis of phaeohyphomycosis remains challenging. The clinical presentation of multiple subcutaneous nodules and fistulized masses on the right upper limb strongly suggests a deep fungal infection. However, the patient's diagnostic pathway was prolonged and included an initial misdiagnosis of chromoblastomycosis. The first biopsy described dematiaceous fungal elements in a granulomatous inflammatory background and reported "sclerotic bodies." In this setting, misinterpretation may occur when pigmented hyphae and yeast-like structures are mistaken for muriform cells, especially outside specialized centers. A later review by an experienced pathologist found no true muriform (sclerotic) bodies, which are pathognomonic for chromoblastomycosis [11]. The confirmation of hyphae by direct microscopy and histopathology supported the diagnosis of phaeohyphomycosis.

Fungal culture became the key step for etiologic confirmation, allowing identification of the agent as *Exophiala spp.* Although culture positivity for dematiaceous fungi may be variable, a positive culture provides etiologic confirmation that histopathology alone cannot offer [22-23]. In this case, diagnostic delay and initial misinterpretation were influenced by the patient's context: living in a remote area with limited access to specialized services and being first assessed by general practitioners with limited training in endemic fungal infections. This reinforces the need to strengthen laboratory capacity and clinical education in low-resource settings.

Treatment-related issues also deserve attention. The initial use of fluconazole and then itraconazole at 100 mg/day highlights the importance of training general practitioners working in rural areas, where many cases of subcutaneous mycoses originate. While studies such as Pagnussat et al. [24] support itraconazole as a first-line option based on in vitro activity against dematiaceous fungi, effective dosing for subcutaneous disease is usually 200–400 mg/day, often divided to improve absorption and bioavailability. The favorable clinical outcome observed after increasing itraconazole to 400 mg/day, with substantial lesion regression and no new fistulas, supports the chosen management and reinforces the importance of early diagnosis and adequate dosing.

In conclusion, phaeohyphomycosis is an emerging opportunistic mycosis with non-specific clinical presentation, which can hinder early diagnosis, particularly in patients without classic immunosuppression. This case underscores the need to include phaeohy-

phomycosis in the differential diagnosis of chronic cutaneous lesions, especially in patients with metabolic comorbidities such as insulin-dependent type 2 diabetes mellitus and hypertension, which may favor chronicity and severity. Direct microscopy was essential to guide antifungal therapy, and itraconazole at an appropriate dose led to clinical improvement.

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