



A case of cutaneous phaeohyphomycosis caused by *Biatrispora mackinnonii*

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ABSTRACT

Phaeohyphomycosis is a fungal infection common in immunocompromised patients such as those with hematologic malignancies, transplant recipients or under prolonged corticosteroid use. Here we describe a rare case of phaeohyphomycosis due to *Biatrispora mackinnonii* in a kidney transplant patient. We confirmed *B. mackinnonii* identity by sequencing of the internal transcribed spaces (ITS) region of ribosomal DNA (rDNA) and achieved a satisfactory therapeutic response with itraconazole administration.

1. Introduction

Phaeohyphomycosis (PHM) is a subcutaneous fungal infection commonly associated with immunocompromised patients and caused by a heterogeneous group of opportunistic fungi [1]. It manifests as four clinical forms: cutaneous, subcutaneous, systemic and cerebral PHM [2]. The clinical characteristics of the subcutaneous form resemble benign neoplasms in the skin and soft tissues like lipoma, sebaceous cyst or neurofibroma; therefore, a conclusive diagnosis of PHM is based on identifying the fungus in tissue samples and body fluids through different laboratory techniques, including microscopic examination, histopathology and molecular identification [3]. Here we described a rare case of cutaneous PHM in a renal transplant patient caused by *Biatrispora mackinnonii*, a dematiaceous fungus found in wood and decomposing plants.

2. Case presentation

A 46-year-old woman, who received a kidney transplant 9 years ago and was currently taking tacrolimus (8 mg/day) and prednisone (10 mg/day) presented to our hospital with a 1-year history of a progressive swelling of the nasal dorsum, consisting of two asymmetric nodules with diameters ranging from 1 to 8 cm, with fibroelastic consistency, painless upon palpation and adhered to the deep planes (Fig. 1 A). No

lymphadenopathy was noted and the patient denied any lesions on the adjacent skin or previous trauma.

Our first diagnostic hypothesis included tuberculosis verrucosa, lacrimal duct obstruction and PHM.

Tomography of the paranasal sinuses revealed two small oval lesions, apparently circumscribed with an aberrant soft tissue located in the superficial planes of the right nasal wing, measuring about 0.6–0.8 cm. Fine needle aspirate from a subcutaneous nodule on the nasal dorsum was sent to mycology laboratory where dematiaceous septate hyphae were seen in 10% KOH mount (Fig. 1 B) (Day 0). The isolate was inoculated on Potato Dextrose Agar and Sabouraud Dextrose Agar and incubated at both 25° and 37° in case of a dimorphic fungus. All tubes grew dark brown colonies (Fig. 1 C) (Day 7). Microculture showed numerous gray sterile mycelium (Fig. 1 D) which hindered morphological identification.

To identify the isolates, Internal Transcribed Spacer (ITS) regions were amplified using ITS4 and ITS5 regions of the fungal 5.8S ribosomal DNA (rDNA) gene. Assembled sequences

Were compared against those present in the National Center for Biotechnology Information (NCBI) GenBank® (www.ncbi.nlm.nih.gov/genbank/). The sequence obtained had a coverage of 97,44% of identity with *Biatrispora mackinnonii* (LT796847.1) type strain.

The patient was administered at day seven oral itraconazole 200 mg daily for 6 months and achieved improvement in the lesion after this

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time (Fig. 2). She was also referred to the surgeon for the surgical removal of the nodules. Although a regular follow-up was recommended to assess the long-term response to the therapy, the patient interrupted the follow-up after these 6 months.

3. Discussion

PHM is an opportunistic fungal infection caused by a variety of dematiaceous (pigmented) fungi (over 100 different fungal species). However, this infection is usually unrecognized or misidentified because the etiological agents lack morphological specificity and present polymorphic appearance [4].

Its clinical spectrum varies from local to systemic dissemination. Although uncommon, it can occur in both immunocompetent and immunocompromised hosts but it is more frequent in patients in immunosuppressive conditions, particularly those submitted to solid organ transplantation as kidney transplant patients [5].

Using gene sequencing we identified *B. mackinnonii* as the causative agent in this case. This species was originally classified as *Pyrenochaeta mackinnonii*, but subsequent revision in the classification renamed the genus as *Nigrograna* which was further reduced to its current name *Biatrospora*. *B. mackinnonii* is a saprophyte mostly found in soil or associated with plants, usually encountered in tropical and subtropical areas [6]. To date, this species has been implicated in PHM in renal transplant and keratitis patients [5,7].

Recently, Ahmed et al. showed that 21 strains in the literature responsible for most cases of black grain eumycetoma in Latin America revealed to be *B. mackinnonii* rather than *Trematosphaeria grisea* [8]. The absence of conidiogenesis in isolates from PHM infections has hindered accurate species identification, thus, only recently, due to the advances in molecular biology techniques, we have a rapid and accurate method for detection of unculturable or nonsporulating melanized molds like *B. mackinnonii*, which is essential for disease surveillance and implementation of management strategies.

No standard therapeutic protocol is established for this infection, but posaconazole, itraconazole and voriconazole are known to be active [9, 10]. In addition, two cases of *B. mackinnonii* PHM were treated with itraconazole and/or excision, achieving complete cure [11,12]. Here in our report, we presented a treatment regimen with 200 mg

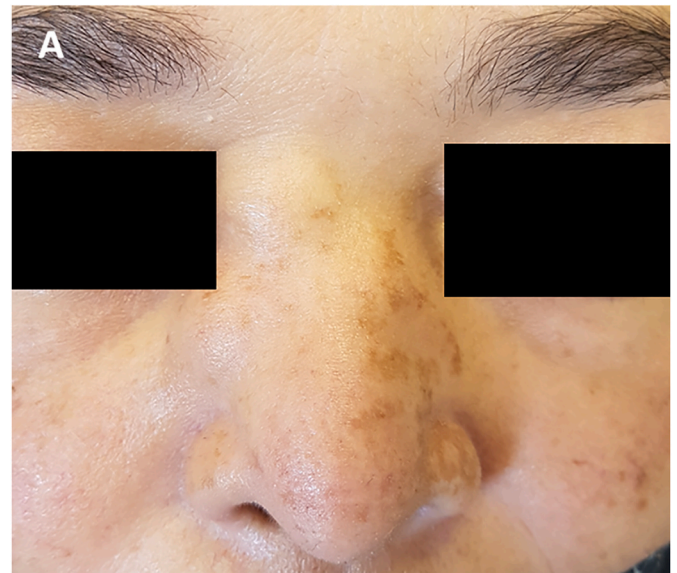


Fig. 2. Lesion aspect after 6 months of treatment with itraconazole (200 mg/daily).

itraconazole/day. Even though we could not confirm sterilizing cure due to the patient noncompliance to the follow-up, we did observe a significant clinical improvement after 6 months of treatment.

In conclusion, it is still a challenge to quickly and accurately identify the causative agent of PHM from a growing list of fungal pathogens recovered from a diversity of clinical specimens. In the last decade, we have been witnessing the increase in the number of opportunistic fungi causing disseminated and subcutaneous infections in immunocompromised but also in immunocompetent patients. Therefore, a rapid diagnosis is crucial for the proper management of these fungal infections. Unfortunately, phenotypic and biochemical identification methods are not efficient to identify fungi with sterile mycelia, which has created an increasing demand for new molecular diagnostic methods for fungal identification.

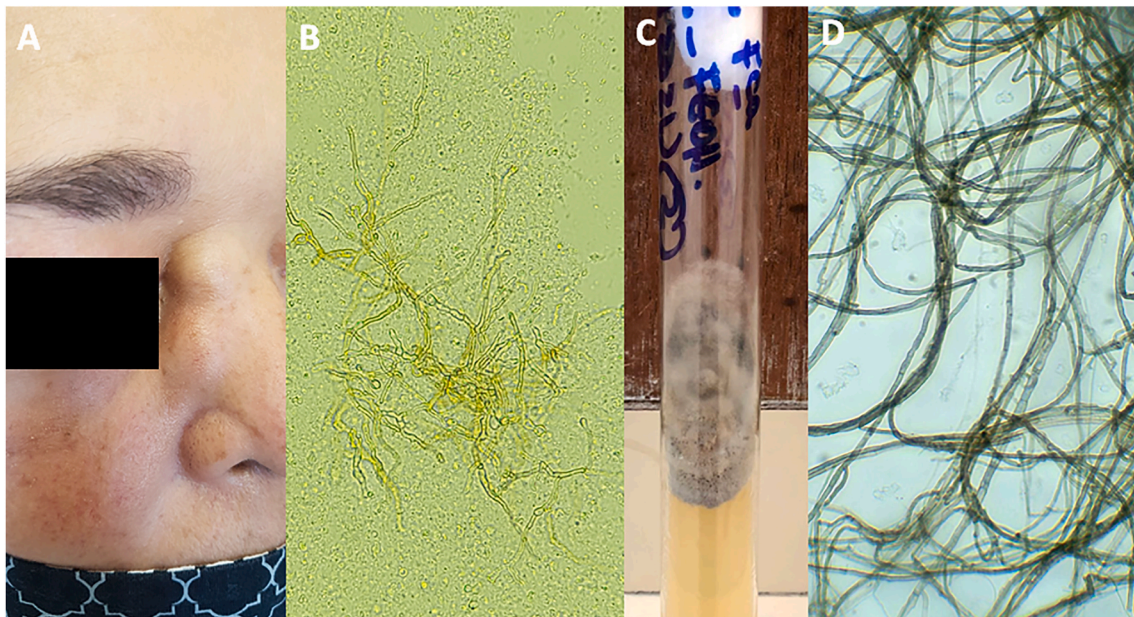


Fig. 1. A. Clinical presentation of asymmetric nodules in nasal dorsum; B. KOH (10%) mount showing dark brown hyphae (400× magnification); C. Culture on Sabouraud dextrose agar culture showed a dark gray mold and D. Microscopic morphology of *B. mackinnonii* from a Riddell slide culture, showing numerous dematiaceous sterile mycelium (400×). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

JV and MGTS wrote the manuscript. GB, APCR, DVMS and GMBDN performed the experiments. All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

Please declare any financial or personal interests that might be potentially viewed to influence the work presented. Interests could include consultancies, honoraria, patent ownership or other. If there are none state 'there are none'

References

- [1] R. Dobiáš, V. Havlíček, [Chromoblastomycosis and phaeohyphomycosis - pathogenesis and laboratory diagnosis], *Klinická Mikrobiol. a Infekční Lékarství* 26 (2) (2020) 69–75.
- [2] S.G. Revankar, D.A. Sutton, M.G. Rinaldi, Primary central nervous system phaeohyphomycosis: a review of 101 cases, *Clin. Infect. Dis.* 38 (2) (2004) 206–216.
- [3] S.R. Jinkala, D. Basu, S. Neelaiah, N. Stephen, S. Bheemanati Hanuman, R. Singh, Subcutaneous phaeohyphomycosis: a clinical mimic of skin and soft tissue neoplasms-A descriptive study from India, *World J. Surg.* 42 (12) (2018) 3861–3866.
- [4] R. Dobiáš, V. Havlíček, [Chromoblastomycosis and phaeohyphomycosis, overlooked fungal diseases], *Klinická Mikrobiol. a Infekční Lékarství* 26 (2) (2020) 54–61.
- [5] T. Aoki, H. Fukuoka, T. Inatomi, N. Horiuchi, K. Kamei, C. Sotozono, A Case of Black Fungal Keratitis Caused by *Biatrispora Mackinnonii*, *Cornea*, 2021.
- [6] S.A. Ahmed, W.W. van de Sande, D.A. Stevens, A. Fahal, A.D. van Diepeningen, S. B. Menken, G.S. de Hoog, Revision of agents of black-grain eumycetoma in the order Pleosporales, *Persoonia* 33 (2014) 141–154.
- [7] A.G. Puing, A. Couture-Cossette, A.X. Wang, C.C. Zygourakis, X. Cheng, B. A. Stevens, N. Banaei, R.A. Novoa, D.Y. Ho, A.K. Subramanian, Simultaneous coccidioidomycosis and phaeohyphomycosis in a kidney transplant recipient: a case report and literature review, *Transpl. Infect. Dis.* 22 (6) (2020) e13365.
- [8] S.A. Ahmed, G.M. González, A. Tirado-Sánchez, L.M. Moreno-López, S. de Hoog, A. Bonifaz, *Nigrograna mackinnonii*, not *Trematosphaeria grisea* (syn., *madurella grisea*), is the main agent of black grain eumycetoma in Latin America, *J. Clin. Microbiol.* 56 (3) (2018).
- [9] A.M. Borman, M. Desnos-Ollivier, C.K. Campbell, P.D. Bridge, E. Dannaoui, E. M. Johnson, Novel taxa associated with human fungal black-grain mycetomas: *emarellia grisea* gen. nov., sp. nov., and *emarellia paragrisea* sp. nov., *J. Clin. Microbiol.* 54 (7) (2016) 1738–1745.
- [10] S.A. Ahmed, G.S. de Hoog, D.A. Stevens, A.H. Fahal, W.W. van de Sande, In vitro antifungal susceptibility of coelomycete agents of black grain eumycetoma to eight antifungals, *Med. Mycol.* 53 (3) (2015) 295–301.
- [11] R. Hughart, M. Merrick, O.T. Adelaja, S.C. Bleasdale, A. Harrington, M. Tsoukas, Cutaneous phaeohyphomycosis caused by *Biatrispora mackinnonii* in a renal transplant recipient, *JAAD Case Rep* 2 (3) (2016) 230–232.
- [12] Y.H. Yu, P.L. Sun, C.H. Lee, C.J. Su, H.C. Tseng, Deep cutaneous fungal infection by Pleosporales: an exceptional pathogen in tropical Taiwan, *J. Dermatol.* 48 (3) (2021) 413–417.