

# Eumycetoma caused by *Cladophialophora bantiana* successfully treated with itraconazole

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A 57-year-old male presented with dermatosis of the dorsum of the foot consisting of tumefaction, deformity and sinus tract formation. The direct examination of exudates as well as the biopsy tissue, demonstrated the presence of black granules. A dematiaceous fungus was isolated from the lesions and was identified by ribosomal DNA sequencing as *Cladophialophora bantiana*. This is the second report of this fungus as an etiologic agent of eumycetoma in humans. Clinical and mycologic cure was achieved after 20 months of treatment with itraconazole at a starting dose of 300 mg/day that was tapered during the course of therapy. The patient's isolate had an itraconazole MIC of 0.012 µg/ml.

**Keywords** Eumycetoma, mycetoma, *Cladophialophora bantiana*, itraconazole, phaeohyphomycosis

## Introduction

Mycetoma is a subcutaneous infection that may be divided into two groups based on its etiology, i.e., actinomycetoma, which is caused by filamentous bacteria, and eumycetoma, caused by fungi. The agents of the latter may be either hyaline or dematiaceous fungi [1,2]. Mycetoma tends to be more frequent among farmers as a result of local trauma and exposure to the potential etiologic agents during their work activities. The prognosis of each case depends on the following three factors; the causal agent and its resistance to antimicrobial agents, the clinical location, and the progression and degree of tissue involvement [3,4].

This is the second report in humans involving *Cladophialophora bantiana* as the etiologic agent of mycetoma; this fungus is one of the most important etiologic agents of phaeohyphomycosis [5]. Clinical and

mycological features of this case are reported here, as well as the patient's excellent response to treatment.

## Case report

A 57-year-old male freight truck driver, resident of Mexico City, presented with a dermatosis involving the right leg at the dorsum of the foot. The lesion consisted of a swollen area, deformation, nodules, draining sinuses with thread-like material (black granules), as well as retractile scars. The dermatosis had begun three years ago, with progressive swelling of the region and occasional pain. Prior treatments included naproxen, a non-steroid anti-inflammatory drug (NSAID) and other unspecified medications. The presumptive clinical diagnosis was that of mycetoma (Fig. 1).

A direct examination of clinical material from the mycetoma using KOH (10%) demonstrated multiple black granules, approximately 500–1,000 µm in size. The granules were composed of septate, branching, dematiaceous hyphae and vesicles (Fig. 2). Exudates from the fistula were cultured on Sabouraud dextrose agar (SDA) and Sabouraud dextrose agar plus antibiotics (Mycosel) resulting in the recovery of *Cladophialophora bantiana*. The fungus was then maintained on SDA and potato dextrose agar (PDA). The isolate was identified by

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**Fig. 1** (a) Mycetoma baseline. (b) Mycetoma cured after 12-month follow-up.

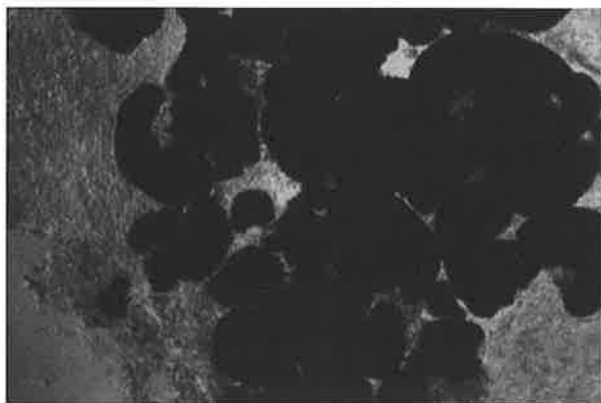
amplification and sequence analysis of ribosomal DNA at the Centralbureau voor Schimcultures (CBS) and maintained at this facility as CBS dH 123392 (Fig. 3).

Tissue sections showed a dense lymphohistiocytic inflammatory infiltrate with plasma cells, multinucleated giant cells, and numerous neutrophils in the dermis. A granule was identified in the deep dermis that was composed of clusters of pigmented hyphal cells (Fig. 4).

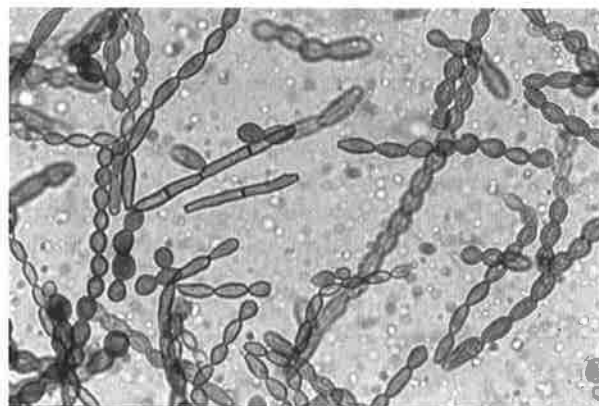
Laboratory tests consisted of a complete blood cell count, blood chemistry and liver function tests all of which were within normal limits. X-rays of the foot showed no bone involvement. Animal studies were conducted by direct inoculation of *cfw1*-mice, without

evidence of neurotropic activity. *In vitro* susceptibility testing was performed on CBS 123392 using the CLSI protocol M38 (NCCLS) [6,7]. Semisolid agar (Brain heart infusion+agar 0.5%, pH 7.4) was used with a conidial suspension ( $0.1 \times 1,000$  CFU/ml) made from a 5-day-old culture. The results at 35°C after 96 h of incubation were: ketoconazole (MIC = 0.20 µg/ml), itraconazole (MIC = 0.012 µg/ml), and terbinafine (MIC = 0.080 µg/ml).

Treatment with itraconazole, 300 mg/day was started, with good clinical response at 11 months of therapy. Owing to the excellent response, the dose was tapered from 300–100 mg/day, until the patient completed 20 months of treatment. Liver function tests



**Fig. 2** Multiple black granules, composed of septate, branching dematiaceous hyphae (KOH 10%, 10 ×).



**Fig. 3** *Cladophialophora bantiana*. Conidia acropetal composed of long chains (Lugol 40 ×).

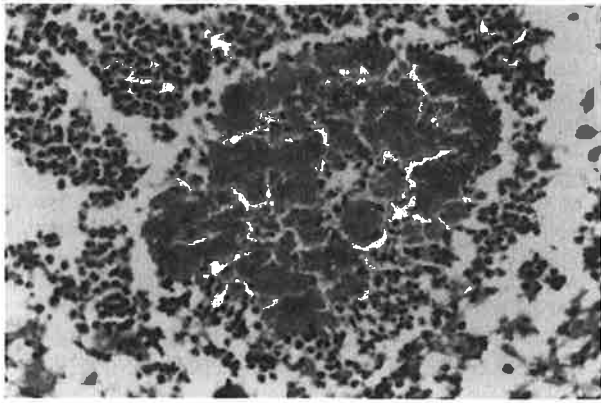


Fig. 4 Histopathology showing a granule composed of pigmented hyphae cells (PAS, 60 ×).

were monitored throughout the treatment period at 4-month intervals, with no alterations. After 18-month follow-up, the patient is still clinically and mycologically free of infection.

## Discussion

Mycetoma most frequently occurs in tropical regions of the world. The causative organism enters through local trauma associated with soil-contaminated material [1,2,4]. Eumycetoma is an infection caused by several different fungi of a broad phylogenetic diversity. Clinically, it is defined by the triad of tumefaction, draining sinus tracts, and the presence of organized hyphal structures known as granules, grains, or sclerotia. These structures consist of aggregated hyphae having a distinct internal architecture, with or without a cement-like matrix [3,4].

*Cladophialophora bantiana*, a dematiaceous fungus, has been known for many years [1–3,5–9]. There are many reports in the literature describing this fungus as the etiologic agent of central nervous system [10–12] infections that have a very poor prognosis. In other cases, the fungus has caused infections involving the skin, particularly subcutaneous tissue, where there is a better prognosis [5,13–15].

There are only two case reports of eumycetoma caused by *C. bantiana*. The first case, described by Guillot *et al.* [16], involved a dog. *C. bantiana* was identified by its microscopic characteristics, and by amplification and sequence analysis of ribosomal DNA. The authors believed that the predisposing factors were poisoning and subsequent treatment with corticosteroids. A good response was observed with the combination of Itraconazole and 5 flurocytosine.

The second case was described by Werlinger and Yen-Moore [17] in a 31-year-old patient with a history

of trauma and systemic lupus erythematosus who was on corticosteroid therapy. The dermatosis involved the back and shoulders. The authors report the presence of black granules and hyphae in tissue leading to their diagnosis of phaeohyphomycosis. This case is important as it shows a continuum in the morphology from mycetoma and phaeohyphomycosis. The patient was successfully treated with fluconazole and itraconazole.

The present case is a classic example of eumycetoma. At first, the etiologic agent was identified as *Cladophialophora carrionii* but after amplification and DNA sequence analysis it was re-identified as *C. bantiana*. This is the third case in the literature which describes mycetoma caused by *C. bantiana* and the second reported in humans. Our patient didn't have any obvious predisposing factors and was immunocompetent [16,17].

In conclusion, the case we are reporting deals with an eumycetoma of the foot, with minimum swelling and multiple sinus tracts, few symptoms and non-osteolytic activity despite its chronic evolution (3 years). Determining the endemic region where the patient acquired the infection was impossible because he traveled throughout Mexico and did not recall a history of trauma.

Our patient responded very well to therapy, although most eumycetomas are considered to have a poor prognosis [18–20]. Other eumycetoma reports have described the same therapeutic response to the triazole, itraconazole, as well as its use in cases of phaeohyphomycosis [15,22,23,24]. It is important to remember that this antifungal agent is fungistatic, and that the outer cells of the granule hinder the entry of the antifungal agents into the structure. Despite the fact that treatment went on for a total of 20 months, no liver alterations were observed. The patient has been followed for over 2 years, with clinical and mycological cure.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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