Onychomycosis due to *Chaetomium globosum* with yellowish black discoloration and periungual inflammation

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**ABSTRACT**

Onychomycosis is usually caused by dermatophytes, although also other filamentous and yeast-like fungi are associated with nail invasion. *Chaetomium* is an environmental genus of ascomycetes exhibiting a certain degree of extremotolerance. We report the first case of onychomycosis in a 46-year-old woman in China caused by *Chaetomium globosum*. The patient showed yellowish black discoloration with periungual inflammation on the left first toenail. We confirmed the causative agent, *C. globosum*, by KOH mount, culture, micromorphology and DNA sequence analysis.

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**1. Introduction**

The large genus *Chaetomium*, belonging to Ascomycota – Sordariomycetes comprises melanized, ascosporulating fungi that inhabit soil, dung and plant debris as a saprobe. The fungi are commonly encountered in indoor environments and show a certain degree of extremotolerance [1]. Although *Chaetomium* species are widely distributed, human and animal infections are uncommon. The prevalent species in clinical settings is *C. globosum*, a rare agent of subcutaneous infections, invasive pulmonary mycosis and systemic infections in immunocompromised patients, as well as onychomycosis in healthy subjects [2,3].

Only a few cases of onychomycosis induced by *C. globosum* have been reported so far. Here, we report the first case of onychomycosis caused by *C. globosum* with periungual inflammation that was confirmed by clinical findings, repeated fungal isolation, light microscopy and sequencing analysis of the rDNA internal transcribed spacer (ITS) region.

**2. Case**

A 46-year-old Chinese woman visited our department in February 2016 (at day 0) with black and yellow discoloration and hypertrophy of the left first toenail with a somewhat painful periungual erythema (Fig. 1). Three years ago (at day – 3 years), the patient first noticed an infection in the first toenail. Physical examination showed that infection destroyed the total nail plate, and the affected nails were discolored, yellow to dark brown to black, with subungual hyperkeratosis. She reported to have a history of doing nail fashion. Physical examination found no other abnormalities. She did not recall a history of long-term administration of steroids or any other drugs. No history of any underlying disease was reported.

Laboratory findings were within normal limits. Serological tests for hepatitis B virus, hepatitis C virus, HIV antibody and anti-nuclear antibodies were negative. Chest radiograph showed unremarkable findings.

**At day 0**, direct microscopic examination of a toenail sample in 20% KOH revealed fungal infection. Light brown-colored hyphae with septa and spores were observed (Fig. 2).

**At day 0**, nail clippings and subungual debris, preserved in sterile saline, were aseptically homogenized and inoculated onto slopes of Sabouraud’s glucose agar (SGA) containing chloramphenicol with and without cycloheximide (0.5 mg/ml), and OA, respectively, at 26 °C. Physiological tests included the growth of the fungus on SGA with cycloheximide (0.5 g/l) at 26 °C and 37 °C, and on OA at 26 °C, 37 °C, 40 °C and 45 °C.

Colonies (SGA and OA without cycloheximide) expanded and grew rapidly, initially velvety, white then turning dark gray to brown, with a reddish diffusible pigment (Figs. 3 and 4). Growth was evident at both 26 °C and 37 °C; no visible growth was observed at 40 °C and 45 °C at day +10. Repeated examination of the toenail sample after a week revealed hyaline, septate hyphae on direct microscopy, and a duplicate culturing on SGA yielded growth of *C. globosum*. No other fungi were isolated.

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**Fig. 1.** A, the left thumb toenail was discolored, yellow brown to black with subungual hyperkeratosis and periungual inflammation at first examination. B, one month after initiation treatment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Fig. 2.** Direct microscopic examination of the toenail sample in 20% KOH revealed fungal infection. Light brown-colored hyphae with septate were observed. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Fig. 3.** A, rapid growing, dark gray to brown colony with aerial mycelium on Sabouraud’s dextrose agar plate after incubation at 25 °C for 1 week. B, Reverse surface of Sabouraud’s dextrose agar plate after incubation at 25 °C for 1 week. C, Rapid growing, dark gray to brown colony with aerial mycelium on Sabouraud’s dextrose agar plate after incubation at 25 °C for 1 week. D, Reverse surface of Sabouraud’s dextrose agar plate after incubation at 25 °C for 1 week. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Microscopically, direct microscopy of the cultured fungi revealed many brown-colored, globose to subglobose perithecia. Ascomal hairs were numerous, usually unbranched, flexuose, undulate or coiled, septate, brownish. Ascospores limoniform in face view, bilaterally flattened, usually brownish with an apical germ pore (Fig. 5).

The identity of the isolated agent was reconfirmed by sequencing of the D1/D2 region of rDNA and compared with reference sequences deposited in Genbank at day +14. The primers sequences as follows: (forward, GCATATCAAAGGCGAGGAAAG; reverse, GGTCCGTGTTTCAGCCGGA). D1/D2 (608 bp) had 100% homology with C. globosum (KC425279.2). The isolated strain showed not only the typical morphological features of C. globosum but also a perfect homology to the D1/D2 sequence of C. globosum in an as yet unpublished database held at CBS (X. Wang, pers. comm.). The isolated agent has been added to the collection of Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College in Nanjing, Jiangsu, under accession number CMCCF 216006.

The in vitro susceptibility of the strain was determined using the microdilution method in accord with the guidelines of the Clinical and Laboratory Standards Institute (CLSI) M38A at day +14. The minimum inhibitory concentrations (MICs) were defined as the lowest concentration at which no growth occurred which led to the following results: itraconazole, 0.125 μg/ml; ketoconazole, 0.25 μg/ml; fluconazole 32 μg/ml; econazole, 0.06 μg/ml; nystatin 4 μg/ml; naftifine, > 4 μg/ml; bifonazole, 0.5 μg/ml and terbinafine 0.5 μg/ml. According to the results of antifungal susceptibility testing, the patient was treated with oral administration of itraconazole 200 mg daily for one week associated with terbinafine cream twice per day. The patient responded well to this combination treatment. After 1 month (day +1 month) of oral therapy with itraconazole, the periungual lesion healed completely (Fig. 1B). Subsequently itraconazole therapy was maintained at a dose of 200 mg per day until day +3 month. The patient has remained available for follow up.

3. Discussion

Chaetomium is a large genus of Ascomycota. Since 1817, when Kunze defined the genus, more than 105 species have been described.
Table 1 Comparison of reported cases with onychomycosis due to Chaetomium globosum.

| Author          | Age | Sex | Geography    | Duration | Site                      | Nail sign                      | Trauma history | Treatment/outcome                                    |
|-----------------|-----|-----|--------------|----------|--------------------------|--------------------------------|----------------|------------------------------------------------------|
| Naidu et al.    | 26  | Male| India        | 1 yr     | Index finger of left hand, thumb third and fourth | Dark brown to sooty black, eroded, dystrophic and brown-black discoloration | None            | None                                                   |
| Stiller et al.  | 83  | Female| India    | 2 yr     | All 10 toenails          | Thickening and brown-black discoloration | None            | None                                                   |
| Hattori et al.  | 57  | Male | Japan       | 2 month  | Lt. 2nd, Rt. 2nd fingernail & Lt. 1st toenail          | Yellow brown to white discoloration | None            | Oral terbinafine 12-week Complete recovery           |
| Aspiroz et al.  | 23  | Male | Spain       | 4 yr     | Lt. 1st toenail          | Yellow-brown discoloration     | Yes            | Oral terbinafine 12-week Complete recovery           |
| Latha et al.    | 25  | Male| India        | 4 month  | Lt. 1st, 2nd, 3rd, 4th toenail & Lt. 1st, 4th toenail & Lt. 1st, 4th toenail | Yellow brown to black discoloration | Yes            | Oral terbinafine daily and topical amorolfin 5%     |
| Kim et al.      | 35  | Male | South Korea | 2 yr     | Lt. 1st, 5th, Lt. 1st, 4th toenail                      | Yellow brown to black discoloration | None            | Oral terbinafine daily and topical amorolfin 5%     |
| This case (2016)| 46  | Female| China    | 4 yr     | Lt. 1st toenail          | Yellow brown to black discoloration | Periungual inflammation | Oral terbinafine daily and topical amorolfin 5%     |

The genus comprised melanized fungi found in soil, on dung, and on plant debris. Several species are regularly encountered in indoor environments [4], which may be due to an extremotolerant character of a number of species [1]. Chaetomium globosum, C. atrobrunneum, C. strumarium, C. perlucidum, and C. funiculum have been confirmed to cause infections in the human host. Most cases were related to systemic mycosis in immunocompromised patients [5–7].

Chaetomium globosum is the most frequently isolated species from patients with superficial mycoses such as cutaneous phaeohyphomycosis and systemic infection in immunocompetent or immunocompromised patients [3,8,9]. To date, six cases of onychomycosis by C. globosum have been published [10–15]. Our report of a toenail infection in an immunocompetent patient deviates clinically from published cases. A comparison with literature data showed that all cases occurred in adults and were chronic, lasting from 2 months to 4 years (Table 1). All six patients showed yellow to brownish discoloration without periungual inflammation. In our case, the infected nail showed yellow to black discoloration.

Predisposing factors in cases of onychomycosis and cutaneous infection mostly involve local trauma [16]. Any process that breaks down the integrity of the horny layer of the nail will facilitate fungal penetration including species that are considered mild opportunists such as Chaetomium species. All patients infected with C. globosum were immunocompetent, and two had a recalled history of trauma. Our case lasted 4 years and occurred only in a single toenail. Our patient had a periungual inflammation, and had a history of nail fashion, which might cause minor nail barrier damage facilitating penetration by C. globosum. Chaetomium species are emerging as a cause of non-dermatophyte onychomycosis, especially in traumatized nails. The spectrum of fungi responsible for nail infections should be expanded to include C. globosum.

The identification of C. globosum was based on micromorphology revealing peritheca with hairy filamentous appendages, and ostioles liberating asci and ascospores. Ascospores are lemon-shaped olive-brown single cells. Sequence analysis of the ITS region of ribosomal DNA is considered necessary for definite identification among the genus Chaetomium [3]. Although the molecular diversity in Chaetomiaeae is unexpectedly large, and taxonomic rearrangements are necessary, our strain was confirmed to be C. globosum (X. Wang. pers. comm.). Our strain showed not only the typical morphological features of C. globosum but also a perfect homology to the ITS sequence of C. globosum in an as yet unpublished database held at CBS (X. Wang. pers. comm.).

Although in some cases, onychomycoses caused by non-dermatophyte molds does not respond well to common treatment, some cases respond well to common treatment. Administration of oral terbinafine to a patient with C. globosum onychomycosis for 3 months completely cured the disease [13]. Other studies with terbinafine and itraconazole appeared to be effective [12]. Likewise, our patient was treated with oral itraconazole 200 mg daily in addition to local application of amorolfin 5% nail lacquer for 1 month, and the patient responded well to the treatment, the periungual inflammation disappeared.

In conclusion, we note that onychomycosis caused by C. globosum is a recurrent feature. If C. globosum is isolated from onychomycosis patients, these should not be disregarded as contaminants but as a potential causative agent requiring further mycological studies.

**Conflict of interest**

There are none.

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