

## 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

### 1. Introduction

The large genus *Chaetomium*, belonging to Ascomycota – Sordariomycetes comprises melanized, ascospore-producing 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 of 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.

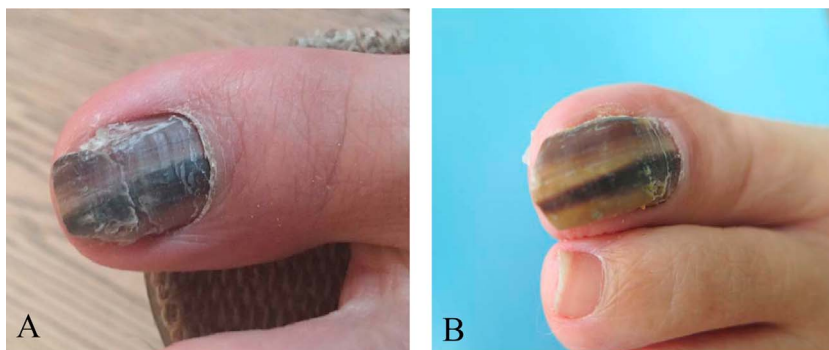
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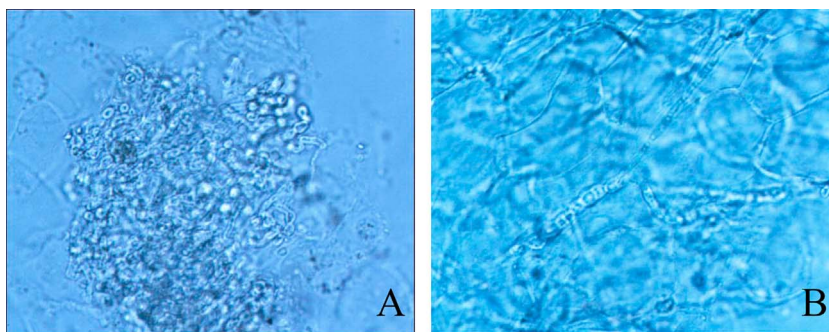
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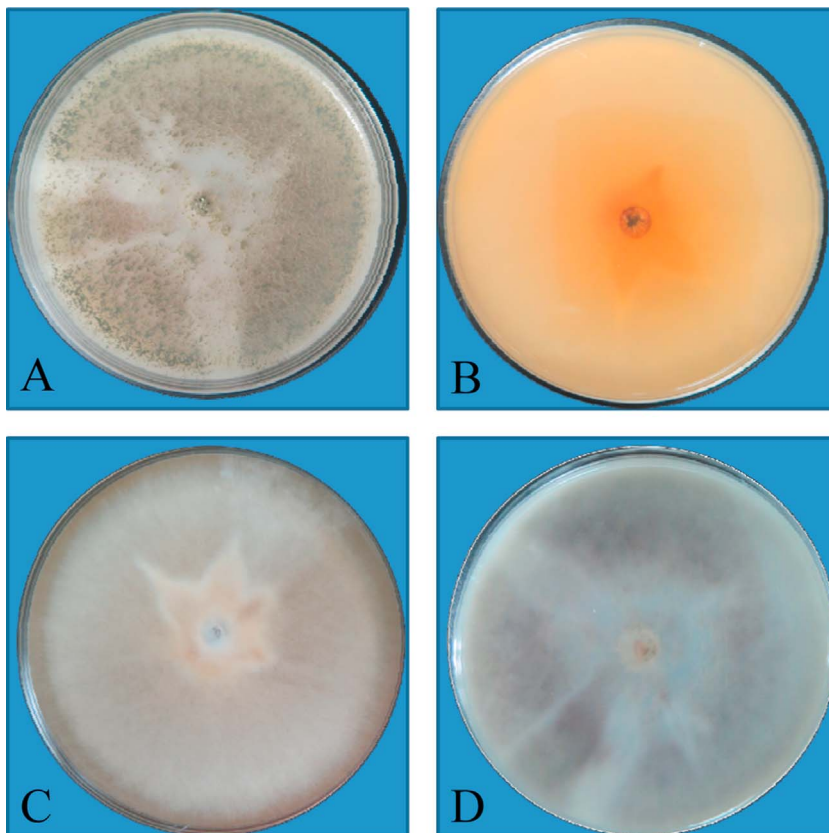
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**Fig. 1.** A, the left thumb toenail was discolored, yellow brown to black with subungual hyperkeratosis and periungual inflammation at first examination. B, one month after initiation treatment. (For interpretation of the references to color in this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



**Fig. 4.** Colonies expanded and grew rapidly, which were initially velvety white then turned to dark gray to brown with reddish diffusible pigment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

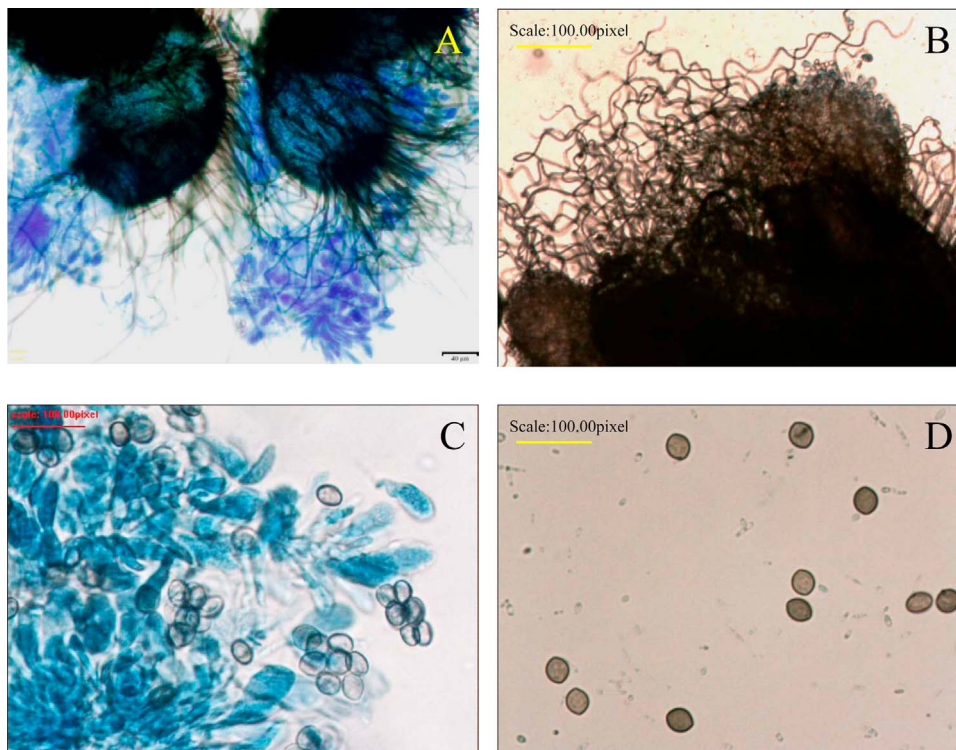
Microscopically, direct microscopy of the cultured fungi revealed many brown-colored, globose to subglobose perithecia. Ascomal hairs were numerous, usually unbranched, flexuose, undulate or coiled, septate, brownish. Ascospores limoniform in face view, bilaterally flattened, usually brownish with an 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, GCATATCAATAAGCGGAGGAAAAG; reverse, GGTCCGTGTTTCAAGACGG). 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 2160006.

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.



**Fig. 5.** A, Close-up view of perithecium which demonstrates ostioles and contains asci and single-celled ascospores (Lactophenol cotton blue stain, ×200). B, C, Large, dark brown to black, flask shaped perithecia with hair-like filamentous appendages (Lactophenol cotton blue stain, ×400). D, Brown-colored septated hyphae and lemon-shaped ascospores (Lactophenol cotton blue stain, ×400). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 1**  
Comparison of reported cases with onychomycosis due to *Chaetomium globosum*.

Author	Age/sex	Geography	Duration	Site	Nail sign	inflammation	Trauma history	Treatment/outcome
Naidu et al. [10]	26/Male	India	1 yr	Index finger of left hand, thumb third and fourth	Dark brown to sooty black, eroded, dystrophic	None	None	None
Stiller et al. [11]	83/Female	India	2 yr	All 10 toenails	Thickening and brown-black discoloration	None	None	None
Hattori et al. [12]	57/Male	Japan	2 month	Lt. 2nd, Rt. 2nd fingernail &, Lt. 1st toenail	Yellow brown to white discoloration	None	None	Oral itraconazole
Aspiroz et al. [13]	23/Male	Spain	4 yr	Lt. 1st toenail	Yellow-brown discoloration	None	Yes	Oral terbinafin 12 week Complete recovery
Latha et al. [14]	25/Male	India	4 month	All Rt. fingernails	Yellow brown discoloration	None	Yes	Oral itraconazole 100 mg for 6 mo
Kim et al. [15]	35/Male	South Korea	2 yr	Rt. 1st, 5th, Lt. 1st, 4th toenail	Brownish yellow	None	None	Oral terbinafine daily and topical amorolfine 5% nail lacquer.
This case (2016)	46/Female	China	4 yr	Lt. 1st toenail	Yellow brown to black discoloration	Periungual inflammation	Yes	Oral itraconazole+lacquer

Lt: left, Rt: right.

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 phaeohiphomy-cosis 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 Chaetomiaceae 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 itraconazol 200 mg daily in addition to local application of amorolfine 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.

### Acknowledgements

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