

Two Cases of Superficial Fungal Infection Caused by Non-*Albicans Candida* Species Manifest Greenish-black Discoloration

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Abstract: The clinical manifestation of superficial candidiasis varies depending on the infectious sites and causative *Candida* species that brings a great challenge to diagnose or treat without mycological or pathological evidence in clinical settings. Oral mucosal candidiasis and onychomycosis are most common types of superficial candidiasis. Typically, oral mucosal candidiasis manifests as white or erythematous thrush coated on the tongue and other interior oral cavity; and onychomycosis caused by *Candida* spp. presents with thick, fragile, or cracked fingernails or toenails in yellow or white discoloration. Here, we report one case of patient with a black hairy tongue caused by *Candida tropicalis* and one case of greenish discolored onychomycosis caused by *Candida parapsilosis*. The cases of superficial candidiasis with the same discolored lesions were searched in literature and compared with our cases in clinical manifestation, causative pathogen and treatment. These cases highlight the importance of mycological diagnosis for identifying non-*Candida albicans Candida* species (NCAC) in superficial infections to guide an effective therapy.

Keywords: *Candida tropicalis*, *Candida parapsilosis*, onychomycosis, black hairy tongue, nail discoloration

Introduction

Candida spp. is one of the most common causes of superficial and life-threatening systemic fungal diseases. Among the array of superficial fungal infections, notable examples include oral mucosal infections and onychomycosis.¹ *Candida albicans* remains the most common species to cause superficial infections that is in consistence with its popular colonization in mucosal sites.² Approximately half of all healthy individuals are carriers of *Candida* in their oral cavities at a nonpathogenic yeast state.³ The risk factors that favor yeast-to-pathogenic hyphae include broad-spectrum antibiotic therapy, corticosteroids, immune suppression, diabetes mellitus and nutritional deficiencies.⁴⁻⁶ Nevertheless, over the last 10–30 years non-*Candida albicans Candida* species (NCAC) have emerged as significant opportunistic human pathogens. Although *C. albicans* remains the predominant causative agent, the NCAC species are increasingly prevalent in specific patient groups, particularly among neutropenic patients.^{7,8}

Their clinical manifestations of superficial candidiasis vary depending on the infective sites and causative *Candida* species, which could bring the great challenge to diagnose sometimes in clinical settings when based only on clinical presentations.⁹ Typically, oral mucosal candidiasis manifests as pseudomembranous thrush that is white coating or curdlike patches on the tongue or other interior oral cavity.² The clinical manifestations of onychomycosis caused by *Candida* spp. often present with thick, fragile, or cracked fingernails or toenails in yellow or white discoloration, which are not distinct from nail infections by dermatophyte species.¹⁰ Here we present two cases of superficial candidiasis who presented with green-black changes on tongue and nails caused by non-*Candida albicans Candida* species.

Case Presentation

Case I

A 50-year-old female patient was initially diagnosed with chronic myelogenous leukemia (CML), and received a genotypically matched hematopoietic stem cell transplantation donated by her brother. Seven months later, she was admitted to our hospital for developed graft versus host disease (GVHD). Patient noted that her tongue started turning black with a hairy appearance at the same time. She had no itch or pain and the lesion had no effect on the movements of mouth and tongue. The patient denies other oral hygiene illness and smoking in the past.

The physical examination revealed a greenish-black discolored patch covering the tongue with elongated “hair” on the dorsal side of tongue (Figure 1). The discolored lesion is 3×5 cm in size and surrounded by irregular white pseudomembranous patches. The hairy appearance is more pronounced in the middle of the dark greenish area. Specimen tissue was taken from the discolored area using a sterile blunt scalpel by alcohol pad and divided into two portions. One portion of specimen was stained with calcofluor-white fluorescent. A large number of spores and hyphae were found under florescent microscopy (Figure 2A). The second portion of specimen was inoculated on blood agar (BA) for bacterial growth and Sabouraud’s Dextrose Agar (SDA) and Potato Dextrose Agar (PDA) supplemented with chloramphenicol for fungal pathogens. All cultures remained in 27°C incubator. By day 3, the large amounts of cream-colored yeast-like colonies appears on SDA and PDA (Figure 2B), but few bacterial colonies were found. The fungal species obtained from isolation underwent identification through sequencing the internal transcribed spacer (ITS) and beta-tubulin (TB) gene, using the following primer sets: ITS1 (5'-TCCGTAGGTGAACCTGCGG-3'), ITS4 (5'-TCCTCCGCTTATTGATATGC-3'), β -tubulin 2a (5'-AATTGGTGCCGCTTTCTGG-3') and β -tubulin 2b (5'-AGTTGTCGGGACGGAATAG-3').¹¹ Following purification, the PCR products were sequenced, and upon a mega blast search of the ITS sequence in NCBI’s GenBank (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>), our isolates were determined to be most closely related to *Candida tropicalis* (GenBank KC422426.1).

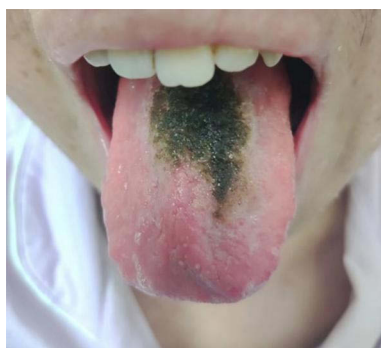


Figure 1 Black hairy tongue on the dorsum of the tongue.

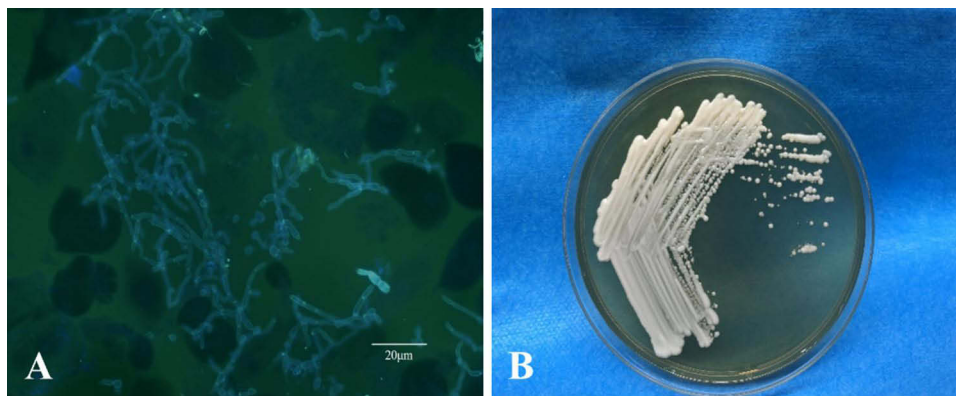


Figure 2 Direct fluorescence microscopy showed blastospores and pseudohyphae (A); On Sabourauds glucose agar at 27°C, cream-colored yeast-like colonies first developed in 3 days (B).

The patient was diagnosed as black hairy tongue caused by *C. tropicalis* and anti-fungal treatment initiated right after diagnosis. Patient was given oral itraconazole 200 mg once a day and the black coloration of the tongue disappeared after 3 days' treatment.

Case 2

A 52-year-old woman reported to the Department of Dermatology with a chief complaint of thickening and discoloration on her right thumbnail, the big and little toenails on her right foot, and the middle and little toenails of the left foot for 5 months duration (Figure 3A). She had no significant past medical condition and drug-used history. There was no nail trauma before the onset of nail infection. The patient received an empirical treatment regimen involving oral itraconazole at a dose of 200 mg twice daily for one week, followed by a 3-week interruption in each 4-week cycle. Notably, after months of treatment, a significant improvement was observed in the lesion on her toenails. However, there was no discernible improvement in her thumbnail. Instead, the affected area on the thumbnail exhibited an increase in size and greenish-black hue (Figure 3B). In addition, a noticeable distal onycholysis, characterized by the detachment of the nail plate, was observed when examining the inferior surface of the discolored nail.

Microscopic examination revealed sub-spherical budding yeast-like cells but no presence of pseudohyphae or hyphae structure in the specimen collected from her right thumbnail (Figure 4A). However, mycelium was easily found on her affected toenails. Based on direct microscopic results, the case was initially diagnosed as onychomycosis caused by dermatophytes.

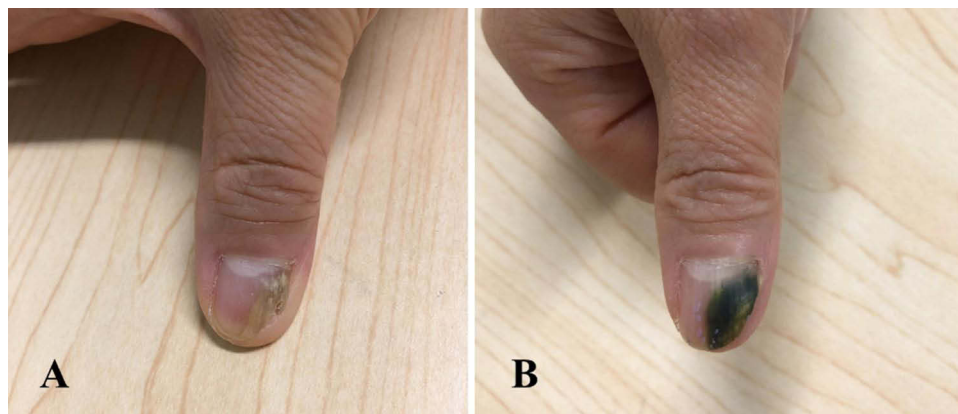


Figure 3 The lesion covered half of the outer edge of the nail plate with yellowish discoloration (A), after 3 months of therapy, and her thumbnail presented with green-black discoloration (B).

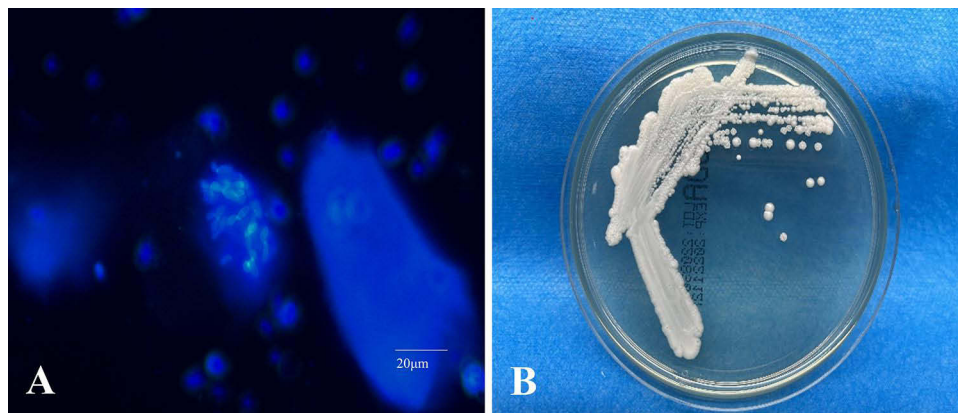


Figure 4 Microscopic examination revealed sub-spherical budding yeast-like cells without pseudohyphae structure (A); Three days later at 27°C, creamy yeastlike colonies appeared on SDA plate (B).

Clinical laboratory tests found no apparent abnormality in blood works. Physical examination showed a diffuse green discoloration on the nail plate extending to the proximal nail fold and distal onycholysis in affected right thumbnail. Specimen was collected and cultured on BA and SDA plate containing chloramphenicol at 27°C. Bacterial culture on BA was negative after 3 days. Repeated fluorescent microscopy examination of the nail samples revealed the same fungal structures as shown in Figure 4A. The repeated cultures yielded the same yeast-like colony appearance (Figure 4B). Despite multiple collection attempts, the analysis consistently confirmed the presence of the same fungus species. Morphological features and molecular sequencing, as described in Case 1, consistently identified *C. parapsilosis* as the causative agent responsible for the infection in the right thumbnail.

Antifungal susceptibility testing was performed following the Clinical and Laboratory Standards Institute M27-A3 protocol. The broth microdilution method was employed to test eight different agents against the isolate strain.¹² The minimum inhibitory concentrations (MIC) were 1.0 µg/mL for itraconazole, 0.125 µg/mL for voriconazole, 1.0 µg/mL for amphotericin B, 0.25 µg/mL for posaconazole, 4.0 µg/mL for nystatin, 1.0 µg/mL for micafungin, 1.0 µg/mL for fluconazole, but greater than 0.5 µg/mL for terbinafine. After the drug sensitivity tests, treatment was changed to oral fluconazole 150 mg weekly for 3 months and nail discoloration faded and the new nail has no sign of relapse at one month follow-up.

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Discussion

We report a case of black hairy tongue caused by *C. tropicalis* in a immunocompromised patient and a case of onychomycosis caused by *C. parapsilosis* in an otherwise healthy patient. Both cases are characterized by greenish-black lesions and good responses to azole antifungal treatment. The greenish-black discoloration caused by *Candida* spp. are less common in oral and skin fungal infection than pigment-producing bacterial and fungal pathogens, such as *Aspergillus* spp. and *Pseudomonas* spp.

Black hairy tongue (BHT) is often recognized by its distinctive black color as shown in Case 1. In Case 1, the painless black hair-like lesion appeared on the dorsum of the tongue anterior to the circumvallate papillae. BHT is a benign medical condition characterized by elongated filiform lingual papillae with typical carpet-like appearance on the dorsum of the tongue. The hairy surface of infected tongue can be accompanied with discoloration ranging from blackish-brown to yellowish green or unpigmented color.⁶ For HBT caused by *Candida* spp., the main manifestations include loss of papillae on the dorsal tongue, erythematous patches and fissuring of the tongue, and may extend to other mucosal surfaces or the corners of mouth (angular cheilitis).¹³ Generally speaking, BHT does not occur on the tip or sides of the tongue. The differential diagnosis for BHT include variant bacterial and fungal infections and unfortunately there are no distinct symptoms to indicate the fungal origin.¹⁴

Review of the medical literature shows that BHT is not uncommon, incidence ranges from 0.6% to 18% in different study populations.^{15,16} The etiology of BHT remains unclear and is likely multifactorial, resulting from combination of local and systemic insults. Many noninfectious predisposition factors are associated with BHT-like manifestation such as smoking, irritants to lead to a poor oral hygiene and cancer such as acanthosis nigricans and oral hairy leukoplakia. Previous clinical observations have linked heavy tobacco use to an increased risk of BHT.^{17,18}

A comprehensive search of online databases, including PubMed and Web of Science, was conducted. In addition, the reference lists of all retrieved articles, including review articles, were examined. The search spanned 2000 to 2022, and the following terms were used: “black hairy tongue”, “black tongue”, “hyperpigmented tongue”, “lingua villosa nigra”, and “hairy tongue”. In total, six cases of *Candida*-related BHT were found in our literature search. The clinical characteristics of patients with *Candida*-related BHT are listed in Table 1. Of the six patients,^{19–24} two were male and four were female. The patients’ ages ranged from 3 months to 106 years old. Four patients with poor oral hygiene had one or two risk factors listed above for BHT, including smoking, drinking alcohol and coffee, and edentulism. The mycological identification found that none of them were caused by *Candida tropicalis*. All six patients responded well to antifungal therapy and full recovery from BHT was achieved with by practicing good oral hygiene. It is worth noting that two articles have pointed out that allogeneic stem cell transplantation is also associated with the occurrence of BHT,^{25,26} the same as our reported Case 1 in this study.

Table I The Cases Diagnosed with Black Hairy Tongue

Authors/ Year (Reference)	Age/Sex	Symptoms	Microbiologic Findings	Treatment	Recovery Time	Possible Risk Factors
Chakraborty and Pulai 2013 ¹⁹	64/M	Black discoloration with hairy appearance of the tongue	<i>Candida albicans</i>	Short course of oral fluconazole	4 days	Right-sided complete hemiparesis
Kobayashi et al 2010 ²⁰	77/F	Yellowish brown to brownish black discoloration on the dorsum of the tongue	<i>Candida albicans</i>	Oral fluconazole	Subsided promptly	None
Sheikh et al 2011 ²¹	53/F	Black discoloration of the tongue	Tongue scrapings confirmed <i>Candida</i> infection	Short course of fluconazole	7 days	Smoking and drinking alcohol and coffee
Dimitrios et al 2012 ²²	81/F	Black hairy tongue	<i>Candida glabrata</i>	Brushing of the tongue with a soft toothbrush and topical tretinoin	7 days	Smoking and drinking alcohol and coffee
Kriem et al 2017 ²³	106/F	Black symmetric discoloration of the tongue that looked spongy	<i>Candida albicans</i> , <i>Candida krusei</i> , <i>Staphylococcus</i> <i>saprophyticus</i> .	Oral fluconazole	4 days	Poor oral hygiene and did not have dentures
Ramsakal and Mangat 2007 ²⁴	24/M	Black discoloration and hairy appearance of the tongue	Throat culture was positive <i>Candida</i> <i>albicans</i>	Discontinued doxycycline and underwent treatment with a short course of fluconazole	3 days	None
Case I	50/F	Painless thick greenish- black coating on her tongue	<i>Candida tropicalis</i>	Itraconazole 100mg bid 3 days Amphotericin B 10 mg qd 2 days	3 days	Graft-versus- host disease

Use of systemic and local medications may induce or exacerbate BHT condition. Antibiotics associated with this disorder are linezolid, penicillin and erythromycin, and others.^{27–29} Yet the mechanisms to develop black hairy tongue with antibiotics are not known. It may be possible that antibiotic use alters the oral microbiota. Furthermore, the pronounced anatomical alteration in the filiform papillae may predispose the patient to trap foreign material or stimulate certain microbial overgrowth, leading to the typical color change in patients with BHT. One bacterium capable of producing the aforementioned findings is the porphyrin-producing black-pigmented gram-negative anaerobic rod *Porphyromonas gingivalis*, known for its implication in chronic periodontitis.^{30,31} However, this is an entirely speculative theory and which fails to explain the cases where the discoloration is yellow, green, or light color texture. Although it is not as common as *C. albicans*, *C. tropicalis* can be isolated from the oral cavities. However, the specific mechanism of microflora such as *C. tropicalis*-related to that found in a greenish-black discolor BHT is still unclear.¹⁹

Onychomycosis clinically presents with nail discoloration in a spectrum of white, yellow, and brown where the fungus is dense. The nail separation from the nail bed (onycholysis), brittleness, nail thickening, and subungual accumulation of scale are common symptoms.¹⁰ For onychomycosis caused by *Candida* spp., the discoloration also ranging from white, yellow to yellowish brown.⁹ The clinical presentation of Case 2 caused by *C. parapsilosis* presented with an atypical color from those described in the literature. The greenish-black discoloration only appeared in the right thumbnail, but not in other nails. Although such dark discoloration by *C. parapsilosis* has been reported previously,³² the

exact mechanism remains unclear. However, previous studies have found melanin presence in conidia of *C. parapsilosis*,³³ which may explain the dark colored lesions in this case.

A search of the online databases PubMed and Web of Science as well as the reference lists of all retrieved articles was performed for articles published from 2000 to 2022. The search terms were “Candida & Onychomycosis & green”, and “Candida & Onychomycosis & black”. After a review of the literature, it was found that some cases showed green or black skin and nail lesions caused by *Candida* spp. that are similar to Case 2.^{32–40} Of note is fungal melanonychia, a rare nail disorder that presents as a longitudinal dark pigmentation in the nail plate. The causative *Candida*-associated fungal melanonychia were *Candida albicans* and NCAC.^{33–40} These isolated *Candida* were considered to be the cause of the discoloration rather than a colonized status.^{41,42} In addition, some researchers have even introduced a term, viridionychia to specifically describe fungal etiology-associated green nail syndrome,³² which differs from chloronychia with bacterial-associated green nail syndrome. Interestingly, the proposed viridionychia term was based on a fungal nail infection caused by *Candida parapsilosis*. Although some *Candida* spp. such as *C. parapsilosis* may produce more melanin than others, melanonychia may commonly results from the activation of host melanocytes within the inflammatory area of the nailfold.⁴³

It is worth mentioning that, green nail syndrome may be differentiated from a paronychia infection due to bacterial pathogens such as *Pseudomonas aeruginosa*, or mixture of bacterial and fungal pathogens, which often results in the same green discoloration on the nail plate.^{44,45} *P. aeruginosa* is a gram-negative coccobacillus with a predilection for moist, aquatic environments. It produces pyocyanin and pyoverdine, which are pigmented virulence factors that give its characteristic blue-green color in green nail syndrome.⁴⁶ However, when *P. aeruginosa* is associated with green nail discoloration, it is usually described as Goldman–Fox syndrome.⁴⁷ To the best of our knowledge, fungal-associated green nail syndrome are less common than bacterial origins.⁴⁸ This may be related to the fact that *P. aeruginosa* has been shown to inhibit fungal growth,⁴⁹ which may be more meaningful in the case of mixed yeast and *P. aeruginosa* infection. Studies have suggested the use of nail dermoscopy for identifying the mixed infection.

The discolored thumbnail in Case 2 responded to fluconazole treatment after failure with itraconazole. Since we the yeast-like colonies were not identified in the specie level, this non-itraconazole response suggest a possible of mixture of *Candida* spp. in thumbnail. Thus, the individual nail specimen collection may be necessary, especially when treatment responses are significantly different among nails involved. In such cases, the nonresponsive nails need to be reevaluated for antifungal regimen after repeat fungal identification. When *C. parapsilosis* is identified, an oral treatment by terbinafine or fluconazole in combination with topical application amphotericin B are recommended. As our susceptibility tests shown in Case 2, *C. parapsilosis* is sensitive to above drugs.⁵⁰

Conclusions

In conclusion, the distinct greenish-black discoloration was found in *C. tropicalis* – and *C. parapsilosis* – caused superficial candidiasis in our and other reports. Immunosuppressive therapy and nail damage could be the risk factors of our two cases, however, fungal or host agents that are responsible for the greenish-black discoloration are unknown but may be due to multiple factors. We could not establish a correlation between *Candida* species and a greenish-black discoloration since the fungal-associated BHT and the green nail syndrome are still rare.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Informed Consent

This study was approved by the Institutional Research and Ethics Committee of Jining No. 1 People’s Hospital to publish the case details (Ethical approval no. 2022-029). All patients provided written informed consent for publication of this case report and any accompanying images. The study was carried out in accordance with the principles of the Declaration of Helsinki.

Consent for Publication

Written informed consent was obtained from the patient described in this report. A copy of the written consent is available by request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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