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REVIEW PAPER

Isolated Cutaneous Granuloma Caused by *Candida glabrata*: A Rare Case Report and Literature Review

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Abstract The incidence of candidiasis due to non-*albicans* Candida species (especially *Candida glabrata*) has significantly increased in recent decades. *Candida glabrata* often invades immunocompromised hosts and causes systemic or mucosal infections, whereas cutaneous infections are rarely reported. We present a rare case of cutaneous infection caused by *C. glabrata* and review all similar cases available in the PubMed database. A patient was admitted to the hospital with a 2-month history of a plaque on the face. Histopathological examination displayed typical infectious granulomas in the deep dermis, and the pathogen was finally confirmed as *C. glabrata* using a series of microbial examinations (fungal culture, biochemical test, and PCR-directed sequencing). The patient was completely cured after 4 months of treatment with oral itraconazole combined with topical terbinafine. We reviewed similar reports of cutaneous infection caused by *C. glabrata*. All the data suggested that an accurate diagnosis of cutaneous candidiasis depends mainly on histological and fungal examinations, especially molecular biological assays. Antifungal agents based on microbial susceptibility tests are the first-line treatment choice for *C. glabrata* infection, but the prognosis might be more dependent on the basic condition of the host.

Keywords Cutaneous granuloma · Candidiasis · *Candida glabrata* · Diabetes mellitus

Abbreviations

PCR	Polymerase chain reaction
AIDS	Acquired immune deficiency syndrome
SDA	Sabouraud agar
H&E	Hematoxylin and eosin
MIC	Minimal inhibitory concentration

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Introduction

The incidence of candidiasis has increased noticeably in recent decades with the expansion of aged populations and immunocompromised patients such as those with AIDS, carcinomas, and stem cell or solid organ transplants. *Candida albicans* is still the main pathogenic species responsible for candidiasis; however, other *Candida* species, especially *C. glabrata*, are showing an increasing incidence [1]. *Candida glabrata* mainly causes systemic or mucosal infections in immunosuppressed patients due to the increased use of prophylactic antifungal treatment [2]. Isolated cutaneous candidiasis is an extremely unusual manifestation of *C. glabrata* infection. Here, we describe a rare case of isolated cutaneous granuloma on the face caused by *C. glabrata*, and we review all similar cases available in the literature.

Case Presentation

A 60-year-old female farmer was admitted to the hospital with a 2-month history of a plaque on the face. Two months earlier, an abrasion developed on her right cheek while she labored in the field, but it was not treated. A few days later, some erythematous papules developed on the site of the injury (Fig. 1). These cutaneous lesions gradually enlarged into an infiltrative plaque (3.5×4 cm^2) covered by filthy crusts, and topical glucocorticoids and antibiotic agents were administered. The patient presented no fever, chills, headaches, arthralgia, or weight loss. Her past medical history was unremarkable, although she had diabetes mellitus for the previous 7 years, and her blood sugar was well controlled with oral medicine.

All the laboratory and imaging examinations were normal, such as complete blood counts, blood chemistry, antinuclear antibodies, tumor markers, microbial serological tests (syphilis, HBV, and HIV), tuberculin skin test, chest X-ray, and abdominal ultrasonography. A skin biopsy was performed for histopathological and microbiological examinations. A pathological section stained with H&E revealed groups of histiocytes mixed with numerous lymphocytes, as well as a few neutrophils and plasmocytes in the dermis, suggestive of an infectious granuloma (Fig. 2a, b). Acid-fast staining and bacterial culture were negative. The fungal culture displayed cream-colored colonies on SDA agar and purple colonies on CHROMagar (data not shown). The pathogenic yeast was finally identified as *C. glabrata* by API 20C AUX Auxacolor (Bio-Rad) and PCR-directed sequencing (GenBank accession number: KY106479.1) as previously described [3, 4].

Since *C. glabrata* has been reported to be more resistant to antifungal drugs (especially azoles) than other *Candida* spp. [5]; broth microdilution testing was performed to evaluate its susceptibility exactly as outlined in CLSI document M27-A2 [5]. Fortunately, the clinical isolate displayed good sensitivity to common clinical agents, which showed a minimal inhibitory concentration (MIC) of 2 μg/ml for fluconazole, MIC of 0.125 μg/ml for itraconazole, MIC of 0.0625 μg/ml for voriconazole, MIC of 0.25 μg/ml for amphotericin B, MIC of 8 μg/ml for terbinafine, and MIC of 0.25 μg/ml for caspofungin. According to the results, the patient was administered oral

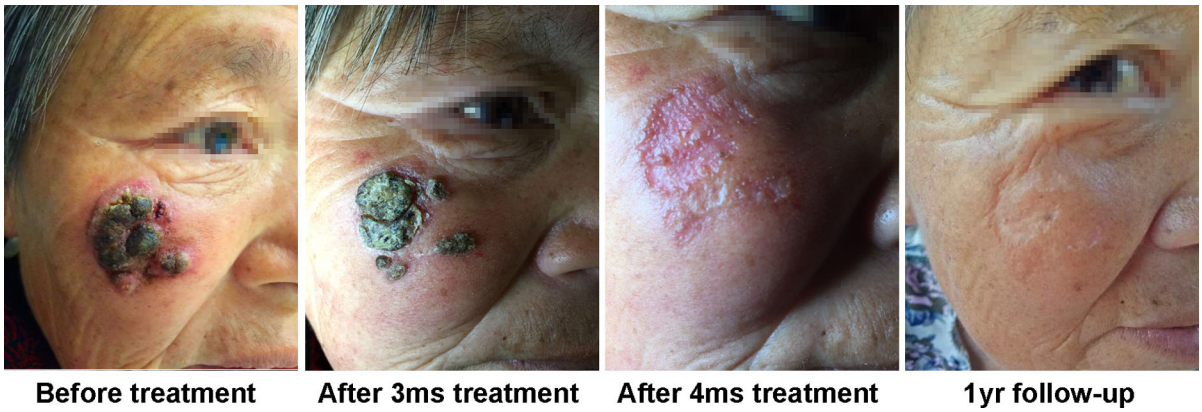

Fig. 1 Facial lesions before and after treatment

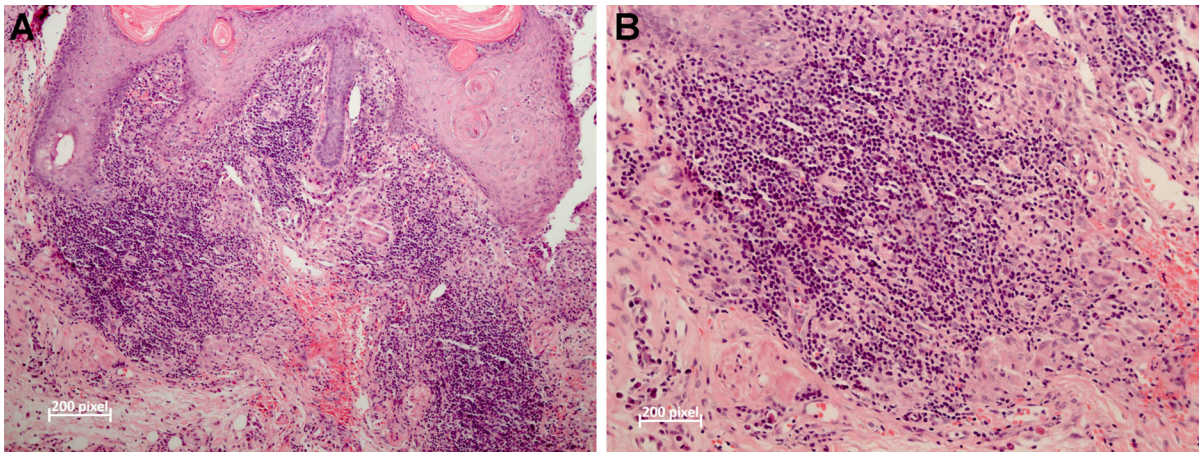

Fig. 2 Histopathological and fungal examinations after skin punch biopsy. **a** (100×), **b** (200×). H&E-stained section revealing histiocytes mixed with numerous lymphocytes and eosinophils in the dermis, suggesting an infectious granuloma pattern

itraconazole (400 mg per day) combined with a topical terbinafine ointment. After 3 months of treatment, the lesions showed remarkable improvement (Fig. 1), and the dosage of itraconazole was reduced to 200 mg per day for an additional month. The patient was followed up for 1 year, and no recurrence was observed (Fig. 1).

Discussion

In recent years, the incidence of candidiasis due to non-*albicans Candida* species has significantly risen with the increasing number of immunocompromised patients. Among these pathogens, *C. glabrata* has emerged as the second most common pathogen responsible for invasive candidiasis after *C. albicans* [1]. *Candida glabrata* often invades abnormal hosts and causes systemic or mucosal infections, such as candidemia or vaginal or oropharyngeal candidiasis [2], whereas cutaneous infections are rarely reported. Here, we describe a rare case of cutaneous candidiasis caused by *C. glabrata* and review all similar cases available in the PubMed database (Table 1).

Candida glabrata is a ubiquitous organism that can colonize the mucosal surfaces of healthy individuals as a component of the normal flora and can also be isolated from contaminated environments [2]. Among the reviewed cases [6–10], a confirmed history of cutaneous injury was shown in patient 1 (facial abrasion) and patient 2 (sunflower stick in her foot) [6], suggesting an exogenous inoculation. The cutaneous infections of the remaining patients probably originated via endogenous dissemination, and the lesions predominantly occurred in non-exposed sites adjacent to colonized areas such as the gastrointestinal and urogenital tracts [7–10]. All the patients had underlying predisposing factors such as diabetes mellitus (5/6) and malignant tumor (2/6). Furthermore, cutaneous candidiasis resulting from endogenous dissemination was more common in patients with poorer health. Thus, *C. glabrata* might be an important opportunistic causal pathogen of cutaneous infection among susceptible hosts, especially people with diabetes.

Cutaneous *C. glabrata* infections have previously been described to exhibit various manifestations, such as abscess, necrosis, and gangrene. For example, a soft tissue abscess was found in patient 2 who had a 5-year history of diabetes that was controlled [6], whereas necrosis and gangrene frequently occurred in more debilitated patients such as those with untreated severe diabetes and/or advanced cancer [7–10]. Intriguingly, our case rarely manifested as slow-growing plaques, which were histopathologically diagnosed as cutaneous granuloma. This phenomenon might be due to her relatively healthy condition, although she had a 7-years history of diabetes. Hayati et al. reported a similar case of cutaneous candidiasis caused by *C. glabrata* in a patients with AIDS [11]. A main distinguishing characteristic of *C. glabrata* is that it has a haploid genome and thus lacks a hyphal/

Table 1 Clinical characteristics of patients with cutaneous candidiasis caused by *C. glabrata*

No.	Age	Sex	Location	Infection type	Basic diseases and complications	Diagnostic methods	Treatment	Prognosis
1	60	F	Face	Cutaneous granuloma	Diabetes mellitus	Histopathological examination and tissue culture	Oral itraconazole and topical terbinafine	Cure (this study)
2	49	F	Foot	Soft tissue abscess	Diabetes mellitus	Secretion culture	Oral fluconazole and sequential caspofungin	Improved (Celik et al. [6])
3	62	M	Arm	Skin and subcutaneous necrosis, candidemia	Gastric carcinoma, combined with bacteremia caused by *Klebsiella pneumoniae*	Histopathological examination and tissue culture	Oral caspofungin and ceftriaxone	Dead (Gugic et al. [7])
4	43	M	Buttock	Soft tissue necrosis, candidemia	Diabetes mellitus (severe), combined with soft tissue *Streptococcus agalactiae* infection	Histopathological examination, tissue and blood culture	Surgical debridement, oral fluconazole and imipenem	Improved (Shindo et al. [8])
5	54	M	Scrotum	Fournier's gangrene, candidemia	Diabetes mellitus (untreated)	Tissue and blood culture	Surgical debridement and oral caspofungin	Improved (Loulergue et al. [9])
6	82	M	Scotum	Fournier's gangrene, candidemia	Diabetes mellitus, bilateral above-the-knee amputations, and rectal cancer	Tissue and urine culture	Surgical debridement and oral fluconazole	Dead (Joshua et al. [10])

pseudohyphal morphology [12, 13]. In Hayati's case, however, pseudohyphae were detected in skin samples, but adequate molecular microbiology and histopathology evidence was not available. Thus, we suspect that this presentation was misdiagnosed as *C. glabrata* infection, and our case might be the first report of cutaneous granuloma caused by *C. glabrata.*

The diagnosis of fungal infection mainly depends on histopathological and microbial examinations. Our case displayed a typical pattern of cutaneous granuloma, but with less neutrophil infiltration. Fungal culture remains the gold standard for the diagnosis of cutaneous candidiasis. However, different candida species have distinct genetic and biological characteristics [1, 12]. Thus, biochemical and molecular biological assays provide greater clinical significance for the identification of the species of pathogenic organism.

Antifungal agents are still the first-line choice for the treatment of cutaneous candidiasis. In our case, the clinical isolate displayed good susceptibility to common clinical antifungals such as azoles and terbinafine. Prompt surgical debridement might have a good auxiliary effect against cutaneous necrosis or gangrene caused by *C. glabrata* infection [8, 9]. However, the general prognosis of cutaneous *C. glabrata* infection might be more dependent on the basic condition and underlying diseases of the host. Our case was cured completely, whereas patient 3 and patient 6 ultimately died of concurrent carcinoma and secondary cardiorespiratory failure, respectively (Table 1) [7, 10].

In summary, we have described a rare cutaneous granuloma caused by *C. glabrata*. Accurate diagnosis of cutaneous candidiasis mainly depends on histological and fungal examinations, and molecular biological assays are more advantageous for identifying the pathogenic species. Antifungal agents based on fungal susceptibility tests are the first-line choice for the treatment of *C. glabrata* infection. The prognosis of cutaneous *C. glabrata* infection might be more dependent on the basic condition and underlying diseases of the host.

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Authors' Contributions YF, WP, GW, YH, YL, WF, and XT contributed substantially to the conception of the study and analysis and interpretation of the data. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interests The authors have no conflicts of interest to report.

Ethics Approval This study was proved by the Committee on Ethics of Biomedicine Research, Zhejiang Provincial People's Hospital.

Informed Consent Informed written consent was obtained from the patient prior to publication of the case details.

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