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A case of refractory onychomycosis caused by Kloeckera apiculata: Successful treatment with itraconazole

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ABSTRACT

Here, we present the case of an otherwise healthy patient, without risk factors, who developed a refractory case of onychomycosis caused by *Kloeckera apiculata*, an uncommon human pathogen. The diagnosis was ultimately confirmed by fungal nail plate culture, histopathology, and PCR. Whereas prior treatments with topical 5 % tavaborole solution, oral terbinafine, and oral fluconazole were ineffective, complete clinical and mycological cure was achieved with a 3-month course of oral itraconazole.

1. Introduction

Onychomycosis is a common fungal infection of the nail unit with a worldwide prevalence of up to 10 % [1]. The infection can be caused by dermatophytes, saprophytic molds, and yeasts [2]. The condition typically presents with progressive thickening and discoloration of one or more affected nails involving the hands, feet, or both. In more than a third of with patients affected with pedal onychomycosis, concomitant cutaneous involvement (tinea pedis) is also present [3].

Kloeckera apiculata is the anamorph of *Hanseniaspora uvarum*, an ascomycetes yeast originally described in 1870 [4]. It is commonly found in many fruits, soil, coffee, mollusks, and is naturally involved in the fermentation of certain wines, beer, and cider [5,6]. Despite its relative abundance in nature, *Kloeckera apiculata* is an exceedingly rare cause of human disease and an even rarer cause of onychomycosis, with only 3 previous cases having been reported [7–9]. Given the rarity of this infection, successful treatment options have not been formerly described.

2. Case presentation

On day 0, a 32 year-old white male presented to dermatology clinic for treatment of persistent thickening and discoloration of several toenails and his right thumbnail for the past 3 years (see Figs. 1 A,B). The patient had no significant past medical history and was otherwise in good health. The patient had previously been diagnosed with a "fungal nail infection" by another dermatologist, although no diagnostic testing had been performed. He had initially been treated with topical 5 % tavaborole solution daily for approximately 6 months with minimal improvement. When the topical treatment proved ineffective, the dermatologist subsequently prescribed a 3-month treatment of oral terbinafine, which resulted in only modest, temporary clinical improvement. Eventually several months later, the dermatologist prescribed a third treatment with oral fluconazole, which was similarly ineffectual.

On physical examination, subungual thickening and whitish discoloration was evident on several toenails and the right thumbnail. Cutaneous involvement was not present. In order to establish the diagnosis, samples of nail plate keratin were trimmed from several affected digits and submitted for fungal culture and histopathological analysis. Histologic analysis of the nail plate specimens showed hyperkeratosis, parakeratosis, and multiple PAS-positive, elongated, septate hyphae and blastoconidia (Figs. 2, 3). Samples of nail plate keratin were also submitted for fungal culture (Labcorp, Burlington, NC). Colonies grown on Sabouraud agar were positive after 1 week of incubation. The colony surface was smooth and the color creamy white. Microscopic examination of the cultured colonies again showed blastoconidia. The culture was initially screened by MALDI-TOF mass spectrometry however the organism in question was not a validated species in the company's proprietary MALDI database at the time.

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Since the specimen could not be identified with MALDI-TOF MS, it was then sent for definitive PCR sequence analysis using a proprietary set of nuclear ribosomal internal transcribed spacer (ITS) region primers specific for yeasts and molds which confirmed *Kloeckera apiculata* as the causative agent.

Given the patient's motivation to improve his nail condition and lack of response to multiple prior treatments, an oral course of itraconazole 200 mg daily for 3 months was prescribed on day +30. At the conclusion of the treatment, the patient noted marked improvement in all affected nails. At 6 months post-treatment with itraconazole (day +300), a follow-up fungal nail culture was obtained and was negative for fungal growth. The patient has had no recurrence of his nail condition in over 12 months of observation (day +480).

3. Discussion

The differential diagnosis for nail dystrophy observed in this patient includes inflammatory, infectious, and traumatic etiologies. Common inflammatory causes of nail dystrophy include psoriasis, lichen planus, and atopic dermatitis [10]. Infections of the nail unit are most commonly fungal in origin, although bacterial infections typically from staphylococci do occur [10]. Most cases of onychomycosis are due to dermatophyte infection with *Trichophyton rubrum* being the predominant pathogen isolated [11]. Non-dermatophyte causes of onychomycosis include molds and yeasts and account for 10–25 % of all cases [11]. In order to differentiate *Kloeckera apiculata* from other yeasts, molecular techniques such as PCR and MALDI-TOF mass spectroscopy are most frequently employed [12,13].

Currently FDA-approved treatments for onychomycosis are stated for those caused by dermatophyte infection only. Approved topical treatments include ciclopirox, efinaconazole, and tavaborole, while approved oral treatments consist of griseofulvin, terbinafine, and itraconazole [14]. Although not specifically indicated, evidence for the efficacy of itraconazole as a treatment for non-dermatophyte causes of onychomycosis including both yeasts and molds has been previously reported [15].

Of the 3 previous reported cases of onychomycosis caused by *Hanseniaspora uvarum*, partial "clinical improvement" was observed in a single patient treated with 40 % urea ointment followed by ciclopirox nail lacquer [9]. Neither complete clinical, nor mycological cure for onychomycosis caused by *Hanseniaspora uvarum* (*Kloeckera apiculata)* has been previously reported.

In summary, this case documents the fourth occurrence of onychomycosis caused by *Kloeckera apiculata* and its first-ever successful treatment with oral itraconazole. Given the patient's previous treatment failures and present durable response, oral itraconazole should be considered as first-line treatment for future cases of nail infection caused by *Kloeckera apiculata*.

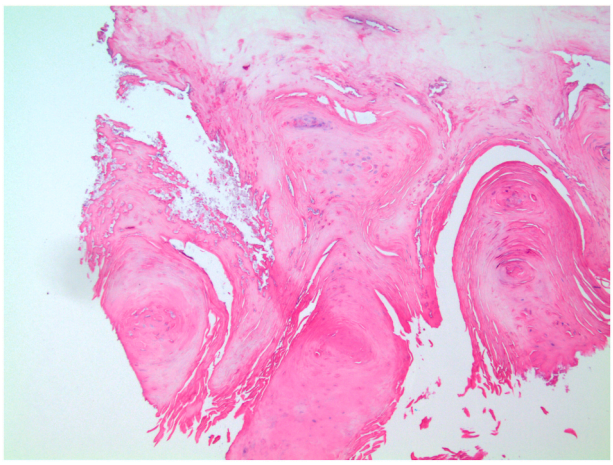

Fig. 2. The nail plate shows hyperkeratosis, parakeratosis, and onycholysis. Hematoxylin & Eosin, original magnification X10.

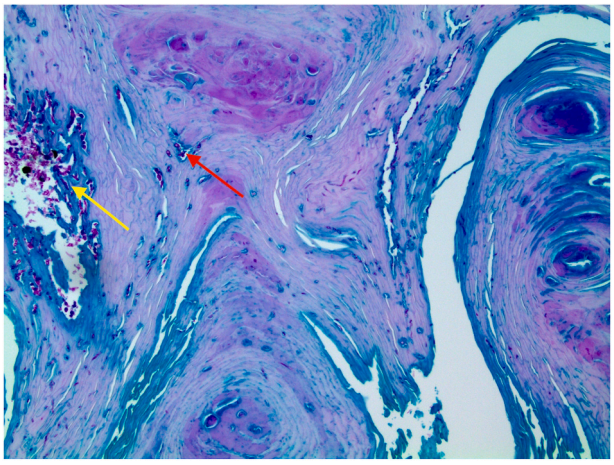

Fig. 3. The nail plate show multiple PAS-positive, sphere-shaped conidia (inset red arrow) and elongated hyphae (inset yellow arrow). Periodic acid-Schiff, original magnification X20. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

CRediT authorship contribution statement

Samantha S. Ehrlich-Fein: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Samir B. Patel:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis,

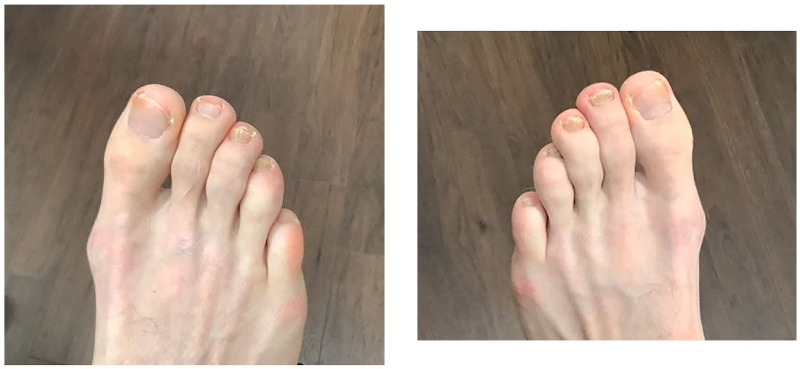

Fig. 1. A,B: Onycholysis and subungual debris are present on several affected digits.

Conceptualization.

Declaration of competing interest

There are none.

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There are none.

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