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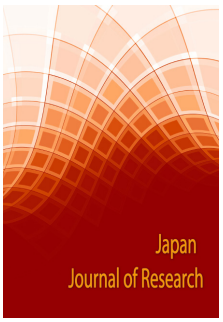
An Unusual Case of Cycloheximide-Resistant Aspergillus Candidus Onychomycosis

Hamza Oualhadj, Soumia Nachat, Mustapha Mezouari, Redouane Moutaj

Laboratory of parasitology-mycology, Avicenna hospital, Cadi Ayyad University, Marrakech, Morocco



Correspondence

Hamza Oualhadj

Laboratory of hematology, university hospital Mohammed VI, Cadi Ayyad University, Marrakech, Morocco
Tel: 00 212 661 061 260
E-mail: houalhadj@gmail.com

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Abstract

Background: *Onychomycosis, a common fungal infection of the nails, poses significant challenges in diagnosis and management, particularly with emerging opportunistic pathogens like Aspergillus candidus. We present a case of onychomycosis caused by cycloheximide-resistant A. candidus, underscoring the importance of heightened awareness and surveillance among medical mycology teams.*

Case presentation: *A 63-year-old male with a history of chronic smoking and type 2 diabetes mellitus presented with lateral onycholysis of the right big toenail. Microscopic examination and culture revealed A. candidus, resistant to cycloheximide. Treatment involved chemical avulsion of the nail plate, systemic terbinafine, and topical amorolfine nail lacquer.*

Conclusion: *Our report signifies the emergence of A. candidus as a significant causative agent of onychomycosis, particularly in individuals with predisposing comorbidities. Vigilance among medical mycology teams is crucial for tracking evolving epidemic trends and optimizing treatment approaches. Continued surveillance and reporting are essential for advancing our understanding and management of fungal infections in clinical practice.*

Introduction

Onychomycosis (OM) is a persistent fungal infection primarily affecting one or multiple nails, commonly triggered by dermatophytes, occasionally by yeasts, and non-dermatophyte molds (NDMs) [1]. It stands as a prevalent condition, comprising around 50% of all nail disorders and 30% of superficial mycoses [1]. Globally, the estimated prevalence of OM ranges from 3% to 26%, showing a continual rise, thus posing a significant public health concern [2]. Various factors, including geographical and climatic variances, age, gender, occupation, socio-economic status, lifestyle, and comorbidities, particularly in immunocompromised individuals, can influence OM prevalence [1,2].

Certain NDMs, once considered mere contaminants, are now increasingly acknowledged as emerging opportunistic pathogens causing OM. Major species include Scopulariopsis, Fusarium, Acremonium, Aspergillus (A.), and Onychocola canadensis [3]. Pathogenetically, OM caused by NDMs may either initiate as a primary event or develop secondarily on nails already compromised by dermatophytes, trauma, or other nail conditions. Typically, these NDMs act as secondary invaders of the nail plate [2,4].

Among Aspergillus species, the three most commonly isolated are A. flavus, A. niger, and A. fumigatus, in descending order of occurrence [3]. A. candidus is considered an exceptionally rare nail pathogen, with only a handful of cases previously reported internationally [5-9]. In Morocco, the documented instance of onychomycosis due to cycloheximide-resistant A. candidus is the first of its kind.

Case report

We report the case of a 63-year-old male patient with a significant medical history, including chronic smoking with 80 pack-years, and type 2 diabetes mellitus managed with oral anti-diabetic medications. Notably, the patient underwent treatment for non-muscle invasive bladder cancer (T1a) three years prior, undergoing transurethral bladder resection followed by intravesical Bacillus Calmette and Guerin (BCG) immunotherapy. Presently, he continues BCG maintenance therapy every six months for three-week intervals.

In January 2022, the patient presented to the medical mycology laboratory of the Avicenne military hospital in Marrakech, Morocco, with suspected onychomycosis. Clinical examination revealed lateral onycholysis of the right big toenail, affecting approximately 25% of the nail surface with total leuconychia in the remaining portion of the nail plate. The onset of symptoms occurred three months earlier,

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manifesting as painful paronychia without pus discharge, gradually progressing to involve the proximal portion of the nail plate and bed (PSO), with subsequent lateral and distal extensions. Notably, other nails, as well as the plantar skin and interdigital spaces, appeared unaffected. The patient recalled undergoing a single pedicure session three months prior when his nails were in a healthy state (Figure 1).

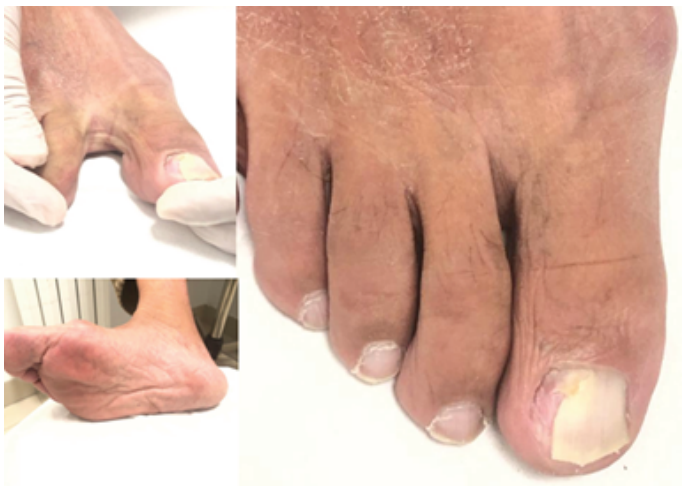

Figure 1. *PSO with onycholysis of 25% of the nail surface and total leuconychia in a diabetic patient with normal plantar skin and interdigital spaces.*

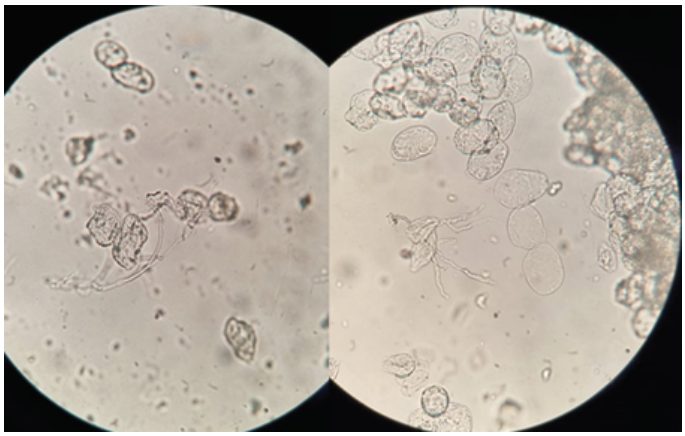

Figure 2. *KOH direct examination showing the presence of broad, septated, and irregular fungal hyphae with acute angle branching on top of the squamous cells. (× 400 magnification).*

Subsequent diagnostic procedures involved multiple scrapings of the affected nail part and the undersurface of the proximal nailfold using a sterile scalpel blade after alcohol disinfection. Microscopic examination with 40% KOH of the freshly collected material revealed the presence of broad, septated, and irregular hyphae with acute angle branching. Cultures were established on Sabouraud's dextrose agar with chloramphenicol (SC) and Sabouraud's dextrose agar with chloramphenicol and cycloheximide (SCC), incubated at 25–30 °C. Following five days of incubation, characteristic pure white mycelial colonies with a white reverse were observed on both SC and SCC media in all inoculated areas. Macroscopic evaluation using magnification revealed spherical white heads. Microscopic analysis via lactophenol cotton blue mount demonstrated predominantly biseriate fruiting bodies, although some were uniseriate. The vesicles were spherical to subspherical, measuring 16–30 µm, with phialides and/or metulae covering their entire surface. Conidiophores measured 600–900 µm with smooth, colorless, and thick walls, while conidia appeared globose with a smooth surface, measuring 2.5–3.5 µm in diameter. Species identification confirmed Aspergillus candidus.

A diagnosis of onychomycosis due to cycloheximide-resistant A. candidus was established based on positive direct examination and successful cultivation of pure cultures on both SC and SCC media in all inoculated areas during three consecutive toenail samplings at one-week intervals.

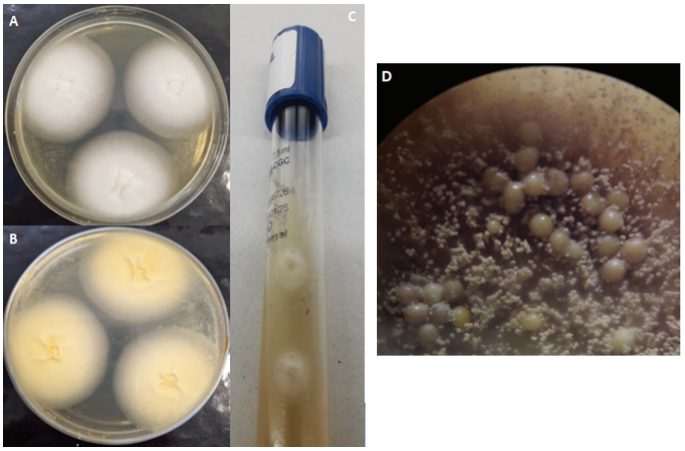

Figure 3. *Macroscopic Morphological Characteristics: White mycelial colonies (A) with a white reverse (B) of Aspergillus candidus in SC medium after 5 days of incubation and in SCC medium (C) after 10 days of incubation at 25 °C. (D) Sclerotia observed using a magnifying glass (15 days).*

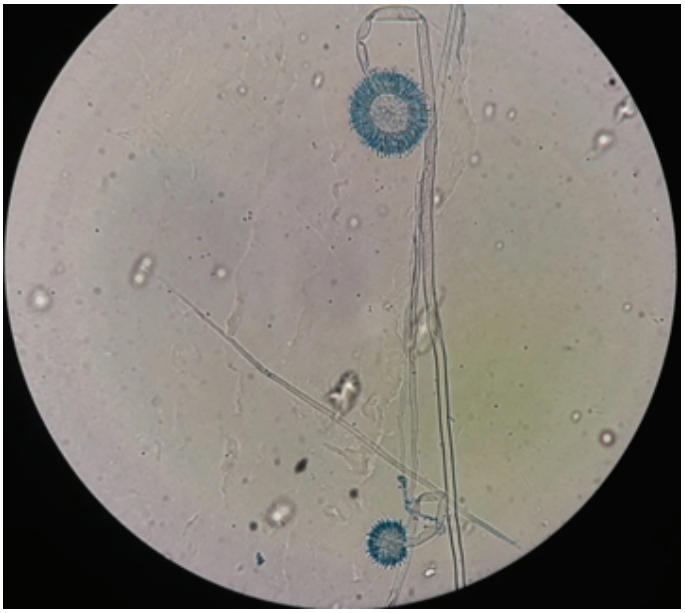

Figure 4. *Lactophenol-cotton blue mount of an Aspergillus candidus colony showing a large biseriate conidial head with globose vesicles and phialides covering its entire surface and a diminutive uniseriate conidial head.*

Discussion

A. candidus, a white-spored species categorized within the "Aspergillus section Candidi," is commonly found in stored cereals, particularly wheat and cereal products such as flour, as well as in grain dust and milled rice [10]. Despite its prevalence in environmental sources, limited reports exist regarding its involvement in human mycoses. These reports encompass diverse clinical presentations, including brain infections [11], solitary aspergillomas in the sphenoid sinus [12], lung abscesses [13], invasive pulmonary aspergillosis [14], and otomycosis [15]. Additionally, A. candidus is implicated in inducing allergic manifestations [14]. Notably, A. candidus exhibits potent immunomodulatory properties through the production of various mycotoxins such as terphenyllines, candidusins, chlorflavonins, kojic acid, and notably xanthoascins, elevating its significance in human pathology [16].

While A. candidus is a rare causative agent of onychomycosis, more commonly implicated species include A. flavus, A. niger, and A. fumigatus [3]. Underlying conditions such as diabetes, peripheral vascular disease, orthopedic trauma, and advanced age predispose individuals to Aspergillus-related onychomycosis [17]. Typically, non-dermatophyte molds act as secondary invaders, targeting nails already compromised by trauma, existing nail disorders, or dermatophyte infections. In our patient's case, factors such as a recent pedicure session causing microtrauma to the nail, age, and comorbidities likely facilitated A. candidus colonization.

Clinically, proximal subungual onychomycosis accompanied by paronychia without pus discharge, exhibiting rapid progression, is characteristic of A. candidus infection, differing from the slower progression seen in tinea unguium [17]. NDM-associated onychomycosis predominantly affects toes and often involves one or two toenails [1]. The presentation of OM due to A. candidus often manifests as chalky white nails with total or striated deep leuconychia [6,18]. Notably, Aspergillus-induced onycholysis may result from the erosive properties of the genus Aspergillus, as observed in deep white onychomycosis cases [6]. Additionally, paronychia frequently accompanies lateral onycholysis in affected individuals [19]. It's noteworthy that a single pathogen can elicit varied clinical presentations of onychomycosis, and conversely [3].

The distinct morphological features of A. candidus aid in its identification. Notably, A. candidus is distinguished by persistently white conidia, setting it apart from other colored Aspergillus species. Additionally, it produces typically fertile vesicles with metulae generally longer than 10 µm, contrasting with A. niveus, which has shorter metulae. A notable characteristic is its inability to grow at 37°C, indicating a predilection for superficial mycoses over invasive forms. Microscopic examination reveals frequently uniseriate conidial heads, varying conidiophore lengths, and the formation of sclerotia by some isolates, serving as survival structures [16].

Confirmation of NDM-induced onychomycosis relies on several criteria, including positive microscopic examination, pure culture isolation, repeated culture positivity, inoculum count, and the absence of isolated dermatophytes [17]. In our patient, these criteria were met, affirming the diagnosis of OM due to A. candidus. Notably, cycloheximide-resistant Aspergillus species are rare, requiring specific culture techniques for detection [1]. In our case, the isolated A. candidus demonstrated resistance to cycloheximide, necessitating culture on SCC medium for growth.

Management of NDM-associated onychomycosis lacks standardized regimens. However, Aspergillus species generally respond well to systemic or topical antifungal therapies, alone or in combination. Notably, pulsed systemic terbinafine has shown efficacy in Aspergillus-related OM cases [18]. For our patient, treatment involves chemical avulsion of the nail plate, systemic terbinafine, and topical amorolfine nail lacquer, with ongoing monitoring.

Conclusion and perspectives

A. candidus emerges as a noteworthy opportunistic pathogen contributing to onychomycosis, particularly in individuals with underlying conditions like diabetes. Our report highlights the first documented case of onychomycosis attributed to cycloheximide-resistant A. candidus in Morocco. Such findings underscore the significance of vigilance among medical mycology teams to track evolving epidemic trends. Continuous surveillance and reporting are vital for enhancing our understanding of fungal pathogens and optimizing treatment strategies in clinical practice.

Statement of ethics

The patient has provided written consent for the publication of his personal data, including personal images.

Disclosure statement

The authors declare that there are no conflicts of interest.

References

1. Kaur R, Kashyap B, Bhalla P. Onychomycosis--epidemiology, diagnosis and management. Indian J Med Microbiol. 2008 Apr-Jun;26(2):108-16. doi: 10.4103/0255-0857.40522.
2. Grover C, Khurana A. Onychomycosis: newer insights in pathogenesis and diagnosis. Indian J Dermatol Venereol Leprol. 2012;78(3):263-70. doi: 10.4103/0378-6323.95440.
3. Raghavendra KR, Yadav D, Kumar A, Sharma M, Bhuria J, Chand AE. The nondermatophyte molds: Emerging as leading cause of onychomycosis in south-east Rajasthan. Indian Dermatol Online J. 2015;6(2):92-7. doi: 10.4103/2229-5178.153010.
4. Gupta AK, Drummond-Main C, Cooper EA, Brintnell W, Piraccini BM, Tosti A. Systematic review of nondermatophyte mold onychomycosis: diagnosis, clinical types, epidemiology, and treatment. J Am Acad Dermatol. 2012;66(3):494-502. doi: 10.1016/j.jaad.2011.
5. Ahmadi B, Hashemi SJ, Zaini F, et al. A case of onychomycosis caused by Aspergillus candidus. Med Mycol Case Rep. 2012;1(1):45-8. doi: 10.1016/j.mmcr.2012.06.003. Jul;
6. Piraccini BM, Lorenzi S, Tosti A. "Deep" white superficial onychomycosis due to molds. J Eur Acad Dermatol Venereol. 2002;16(5):532-3. doi: 10.1046/j.1468-3083.2002.00559_1.x.
7. Cornere BM, Eastman M. Onychomycosis due to Aspergillus candidus: case report. N Z Med J. 1975;82(543):13-5.
8. Fragner P, Kubícková V. Onychomycosis due to Aspergillus candidus. Cesk Dermatol. 1974;49(5):322-4.
9. Kaben U. Aspergillus candidus Link as the cause of onychomycosis. Z Haut Geschlechtskr. 1962;32:50-3.
10. Pitt JI, Hocking AD. Aspergillus and Related Teleomorphs.

In: Fungi and Food Spoilage. Springer, Boston, MA. 2009. https://doi.org/10.1007/978-0-387-92207-2_8.

11. Linares G, McGarry PA, Baker RD. Solid solitary aspergillotic granuloma of the brain. Report of a case due to Aspergillus candidus and review of the literature. Neurology. 1971;21(2):177-84. doi: 10.1212/wnl.21.2.177.
12. Avanzini F, Bigoni A, Nicoletti G. A rare case of isolated aspergilloma of the sphenoid sinus. Acta Otorhinolaryngol Ital. 1991;11(5):483-9..
13. Becker A, Sifaoui F, Gagneux M, et al. Drug interactions between voriconazole, darunavir/ritonavir and tenofovir/emtricitabine in an HIV-infected patient treated for Aspergillus candidus lung abscess. Int J STD AIDS. 2015;26(9):672-675. doi:10.1177/0956462414549035.
14. Ribeiro SC, Santana AN, Arriagada GH, Martins JE, Takagaki TY. A novel cause of invasive pulmonary infection in an immunocompetent patient: Aspergillus candidus. J Infect. 2005;51(4):e195-7. doi: 10.1016/j.jinf.2005.02.020.
15. Yassin A, Maher A, Moawad MK. Otomycosis: a survey in the eastern province of Saudi Arabia. J Laryngol Otol. 1978;92(10):869-76. doi: 10.1017/s0022215100086242.
16. Varga J, Frisvad JC, Samson RA. Polyphasic taxonomy of Aspergillus section Candidi based on molecular, morphological and physiological data. Studies in mycology. 2007;59:75–88. https://doi.org/10.3114/sim.2007.59.10.
17. Noguchi H, Hiruma M, Miyashita A, Makino K, Miyata K, Ihn H. A Case of Fingernail Onychomycosis due to Aspergillus flavus. Med Mycol J. 2016;57(2):E21-5. doi: 10.3314/mmj.57.E21.
18. Gianni C, Romano C. Clinical and histological aspects of toenail onychomycosis caused by Aspergillus spp.: 34 cases treated with weekly intermittent terbinafine. Dermatology. 2004;209(2):104-10. doi: 10.1159/000079593.
19. Hay RJ, Baran R. Onychomycosis: a proposed revision of the clinical classification. J Am Acad Dermatol. 2011 Dec;65(6):1219-27. doi: 10.1016/j.jaad.2010.09.730.
20. Tosti A, Piraccini BM, Lorenzi S. Onychomycosis caused by nondermatophytic molds: clinical features and response to treatment of 59 cases. J Am Acad Dermatol. 2000;42(2 Pt 1):217-24. doi: 10.1016/S0190-9622(00)90129-4. .