International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Onychomycosis Caused by *Aspergillus niger*: A Case Report of An Unusual Etiological Agent

Paulus Mario Christopher[1*], Ketut Kwartantaya Winaya[2]

[1]Faculty of Medicine, Pelita Harapan University, Banten, Indonesia
paulusmarioc[at]gmail.com

[2]Department of Dermatology and Venereology, Faculty of Medicine, Udayana University/Sanglah General Hospital Denpasar, Bali, Indonesia
kkwartantaya[at]yahoo.com

*: Corresponding author

Abstract: ***Onychomycosis is a common fungal disease caused by dermatophytes, yeasts, and non-dermatophyte molds. Aspergillus species are rare and emerging as the etiological agent for toenail onychomycosis. We present a case of a 54-year-old male patient in a stage V chronic kidney disease due to diabetic nephropathy undergoing twice-weekly hemodialysis. The patient showed discoloration of the proximal portion of the left big toenail with subungual hyperkeratosis. Direct microscopy revealed a conidial head with a rather broad long septum and irregular hypha. Based on the growth of modified Saboraud dextrose agar, we concluded the diagnosis of onychomycosis caused by Aspergillus niger. After a 6-week pulse dose treatment and topical antifungal, the disease yielded an improvement.***

Keywords: *Aspergillus niger; aspergillus;* fungal infection; non-dermatophyte molds; onychomycosis

1.Introduction

Onychomycosis (from the Greek word *onychos*–nail and *mycosis*–fungal infection) is a common fungal disease in nails that are produced by dermatophytes, yeasts, and non-dermatophyte molds (NDMs) [1]. According to the Society for Human and Animal Mycology, the term onychomycosis is exclusive for the infections caused by dermatophytes. In contrast, the ones caused by yeasts are known as onyxis; if the etiological organism is *Candida*, they are referred to as nail candidiasis. Those caused by an opportunistic mold are known as nail mycosis [2].

Onychomycoses represent one of the primary nail infections globally, representing up to 50% of all onychopathies. Of this, 33% are related to diabetic patients and 30% to HIV-positive patients [2]. The main NDM species regarded as the etiological organisms of onychomycosis are as follows: *Scopulariopsis*, *Scytalidium*, *Fusarium*, *Aspergillus*, and *Onychocola canadensis* [3]. A principal difference between dermatophytes and NDMs are the non-keratolytic mechanism of NDMs. Due to the latter reason, previous keratin destruction by dermatophytes, trauma, or previous nail disease may provide the NDMs with an optimal condition to invade the nail plate [4].

Several underlying conditions, risk factors, and comorbidities have been identified. Tinea pedis, nail damage, nail psoriasis, age, obesity, diabetes, cancer, immunodeficiency, or peripheral arterial disease can increase the susceptibility to onychomycosis. Another group of patients at risk of developing onychomycosis are patients with chronic kidney disease (CKD). This population is at risk due to the alteration of host defense mechanisms [5], [6].

In the present report, we present a case report of onychomycosis caused by *Aspergillus niger* in a stage V CKD patient due to diabetic nephropathy on twice-weekly hemodialysis in an Indonesian setting.

2.Case Report

A 54-year-old Balinese male was referred to the dermatology and venereology department with subungual hyperkeratosis, dystrophic nail, and significant discoloration that caused color alteration and rough surface areas in the left great toenail in the last six months. Nevertheless, the nail plate remained substantially intact from the structural point of view. The patient was undergoing twice-weekly regular hemodialysis due to diabetic nephropathy for four months before referral. The patient worked as a white-collar worker with a predisposing factor of tight formal shoes for the onychomycosis. The previous history of fungal infection of the ipsilateral foot, nail damage, nail abnormalities, trauma, excessive sweating, or hypertension was denied. On physical examination, dermatological status revealed dystrophic, discoloration, and subungual hyperkeratosis (**Figure 1**). Other nails, as well as the skin of the soles and interdigital webs, were within normal limits.

Direct microscopic examination of nail scrapings and clipping with 20% potassium hydroxide (KOH) revealed a conidial head with a rather broad long septum and irregular hypha, which did not correspond to the hyphae and regular chains of arthroconidia produced in tissues by dermatophytes (**Figure 1**). Portions of the nail scrapings were inoculated in a modified Sabouraud dextrose agar with various antibiotics (chloramphenicol, streptomycin, and penicillin) and a mineral (vitamin B1). A slowly grown black colony was yielded from the inoculation point (**Figure 1**). According to the macroscopic, microscopic

examinations, and culture, an NDM of the *Aspergillus niger (A. niger*) was identified.

According to these results, immediate treatment of the toenail was started with 200 mg oral Itraconazole q12hr (following in a pulse therapy protocol) and 2% Miconazole ointment q12hr was prescribed for six weeks. After six weeks, the patient was examined further, yielding an improved toenail and direct microscopic analysis for fungal elements were not observed.

3.Discussion

Onychomycosis is usually caused by dermatophytes, NDM, and/or yeasts. Onychomycosis caused by NDM comprises 1.45% to 17.6% of total cases, of which one of the etiological agents may be *Aspergillus [*7]. The reported incidence rate varies from 2.6% to 6.1%, with a prevalence of <1 and 35% in the general population and higher among diabetic populations at 71% [7], [8]. *Aspergillus* spp. is a diverse genus (approximately 900 species) of common saprophytic molds found from the soil, air, and decaying vegetation [9]. Among these 900 species, *A. fumigatus, A. flavus, A. niger, A. terreus, A. glaucus, A. chevalieri, A. ustus,* and *A. nidulans* are known to cause infections in the human body [10]. Novel and rarely described species from case reports include *A. tubingensis, A. sydowii, A. alliaceus, A. candidus, A. versicolor, A unguis, A. persii, A. sclerotiorum, A. uvarum, A. melleus, A. tamarii, A. nomius,* and others [11].

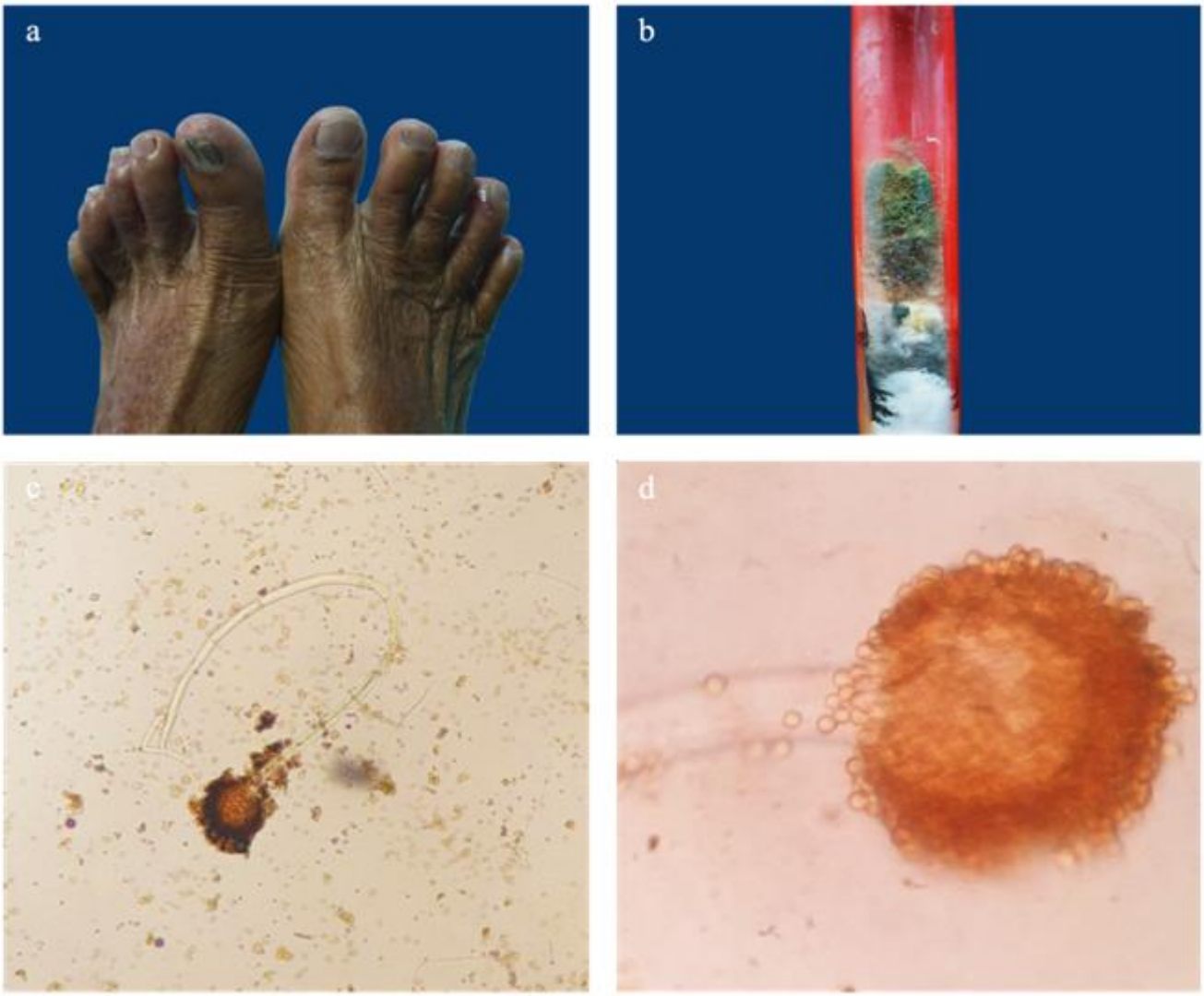

Figure 1: (a) Onychomycosis caused by *Aspergillus niger*: striated deep dark discoloration. (b) Culture of the affected nail on modified Sabouraud dextrose agar, showing *Aspergillus niger*. (c and d) 20% KOH slide preparation of the nail scraping showed a conidial head with a rather broad long septum and irregular hypha (x 400 and x1000, respectively)

Numerous identified risk factors have been associated with *Aspergillus* spp. infections. Following our literature review, environmental factors (outdoor and hospital conditions) and host factors (physical activities and occupational exposure, local humidity and skin maceration, trauma exposure, underlying medical conditions, and medical procedures) are interconnected in *Aspergillus* spp. infection [9]. A higher number of cases are also reported among individuals with occupational exposures, such as vegetable vendors and babassu coconut breakers, diabetics and the elderly [11].

Aspergillus spp. can cause a variety of superficial and cutaneous mycoses (distal lateral subungual onychomycosis [DLSO], proximal subungual onychomycosis [PSO],

otomycosis, and cutaneous aspergillosis) [9]. In onychomycosis, the pathophysiological basis starts under the nail near the hyponychium where spores may have lodged or at the lateral nail folds, or on a diseased nail plate colonized by *Aspergillus* spp. After the initial growth, the infection spreads proximally towards the cuticle leading to a similar appearance in other onychomycosis (discoloration-, thickening-, distortion of the infected nail and flaky). Nevertheless, *Aspergillus* fungus will not spread to the surrounding skin like other fungal agents of nail infection, one of which is due to the non-keratolytic potentials of this NDM. Additional clue of *Aspergillus* spp. nail infection is the colorful pigment produced, e. g., appearing greenish, black, brown or various other shades [11].

Diagnosis of *Aspergillus* spp. nail infection required thorough history taking, physical examinations, and laboratory investigations to differentiate between the etiological agents, antifungal treatment guidance, and complication prevention. NDM onychomycosis may be considered in patients with traumatized or fungal infection in the diseased nail, without associated skin involvement, history of unresponsiveness to commonly used antifungal agents, and other associated risk factors as mentioned above.

Clinical manifestations of *Aspergillus* spp. onychomycosis are usually DLSO, followed by PSO, superficial white onychomycosis (SWO), and total dystrophic onychomycosis (TDO). The toenails are involved 25 times more frequently than fingernails due to the increased exposure to soil, water, and decaying vegetation [11]. According to an Italian investigation, clinical signs and symptoms suggestive of *Aspergillus* spp. onychomycosis include 1) chalky deep white nail, 2) rapid involvement of lamina, and 3) painful perionyxis without pus [12]. Another study revealed that *Aspergillus* spp. nail infection manifested with hard nails (93%), brittle nails (89%), and discolored nails (85%). Yet, the involvement of the surrounding skin is not common [8]. Most patients present with subungual hyperkeratosis and are sometimes associated with subungual dermatophytoma ("fungal ball") formation [11].

Laboratory investigation constituted of potassium hydroxide (KOH) examination of subungual debris, a culture of the nail plate and accompanying debris on Sabouraud's dextrose agar (SDA) with and without antimicrobials, and PAS staining of nail clippings are most beneficial [13]. Additionally, since NDMs' culture from nail specimens does not always translate to causation, Gupta et al. proposed a diagnostic criterion consisting of 6 main criteria; 1) identification of the NDM in the nail by microscopy using KOH preparation, 2) isolation in culture, 3) repeated isolation in culture, 4) inoculum counting, 5) failure to isolate a dermatophyte in culture, and 6) histology. According to previous studies collected, the majority of studies stated at least three criteria to be fulfilled, of which the most common were 1) isolation in culture, 2) KOH preparation, 3) repeated isolation, and 4) dermatophyte exclusion [13]. In our patient, we followed the criteria through the isolation in culture, KOH preparation, and exclusion of dermatophyte as the etiological agent. However, it is worth noting, in less than half of the instances, mycological culture on SDA with or without cycloheximide yields fungal isolates. When KOH preparation and culture are combined, sensitivity is raised to 85.8%. Nail samples acquired from drilling have a greater isolate rate (83%) than those obtained by scraping (67%) [11].

The management of onychomycosis is determined by a few variables, i. e., the severity of nail involvement, presence or absence of tinea pedis, treatment efficacy, and potential adverse effects. Concurrent tinea pedis should always be treated to reduce the risk of cellulitis, particularly in the setting of diabetes mellitus, chronic venous stasis, and other causes of chronic lower-extremity edema. Three treatment modalities may be considered, namely 1) systemic therapy, 2) topical therapy, and 3) mechanical intervention. Nevertheless, treatment options for NDM onychomycosis remain limited, particularly for *Aspergillus* spp. onychomycosis. First, an oral antifungal is necessary for onychomycosis involving the matrix area or when a shorter treatment regimen or the higher possibility of clearance/cure is anticipated. Itraconazole and terbinafine are two systemic antifungal agents regarded in *Aspergillus* spp. (with itraconazole performing better than terbinafine in vitro) [11], [13], [14].

Second, topical treatment may benefit patients with distal nail involvement, WSO, recurrence prevention, and/or contraindicated for systemic treatment. Combination therapy regimens of oral and topical treatment yielded a greater clearance rate rather than monotherapy of oral or topical alone. Topical treatment includes, 1) 40% urea ointment may serve as a chemical nail avulsion for hyperkeratotic nail, 2) topical ciclopirox olamine nail lacquers for SWO, and 3) thymol, camphor, menthol, and oil of *Eucalyptus citriodora* for their in vitro fungicidal activity [14], [15]. Lastly, mechanical intervention, e. g., trimming, debridement, nail bed curettage, and nail abrasion, may aid in speeding up the delivery of medications to the site of action [14]. Other options for refractory cases include laser, surgical avulsion, or chemical removal of the nail utilizing 40% urea compounds together with topical or oral antifungals. In the case of *Aspergillus* spp. total nail avulsion followed by topical antifungal post-operatively is an effective management option for patients with single or oligo-onychomycosis, with a clinical cure rate of 88% and a mycological cure rate of 100% [11], [13], [14], [16].

The disease may significantly impact the individual and other family members. Dystrophic nails may lead to embarrassment, lowering a patient's self-esteem, and may significantly impact quality of life than the severity of the disease itself. Thickened nails may also be painful, causing discomfort in walking and affecting other aspects of daily living [5].

4.Conclusion

Onychomycosis is a prevalent fungal infection with various etiological agents that requires targeted treatment. Due to the slow nature of nail growth, especially in the elderly, treatment takes several months. Drug choice relies on the

etiological agent, the type and severity of onychomycosis, and the patient's comorbidities. High index of suspicion of NDM onychomycosis, especially when the patient is in the elderly age group presenting with predisposing condition like diabetes mellitus must be entertained. All physicians should be aware of the condition and educate the patients, particularly men and the elderly, to notice this condition early. Further understanding of the condition will aid in initiating treatment and prevention of complications, leading to an improved outcome.

Ethical Approval

The patient has signed informed consent and agreed for the publication of their data and any accompanying images as a case report article.

Conflict of Interest

There are no conflicts of interest to declare by any of the authors of this study.

References

[1] Welsh O, Vera-Cabrera L, Welsh E. Onychomycosis. Clinics in Dermatology 2010; 28 (2): 151–159.
[2] Frías-de-león MG, Espinosa-hernández VM, Bonifaz A, Martínez-herrera E. Onychomycosis Due to Aspergillus spp.: a Current Review.2018; .
[3] Singal A, Khanna D. Onychomycosis: Diagnosis and management. Indian J Dermatol Venereol Leprol.2011; 77 (6): 659– 672.
[4] Grover C, Khurana A. Onychomycosis: newer insights in pathogenesis and diagnosis. Indian J Dermatol Venereol Leprol.2012; 78 (3): 263–270.
[5] Elewski BE, Tosti A. Risk factors and comorbidities for onychomycosis: Implications for treatment with topical therapy. J Clin Aesthet Dermatol.2015; 8 (11): 38–42.
[6] Filho AMS, Ventura CG, Criado PR, Del Negro GB, Freitas RS, Luiz OC, et al. Hemodialysis and Kidney Transplantation as Predisposing Conditions to Onychomycosis. Nephron.2017; 137 (1): 38–46.
[7] Kim DM, Suh MK, Ha GY, Sohng SH. Fingernail onychomycosis due to Aspergillus niger. Ann Dermatol.2012; 24 (4): 459–63.
[8] Wijesuriya TM, Kottahachchi J, Gunasekara TDCP, Bulugahapitiya U, Ranasinghe KNP, Neluka Fernando SS, et al. Aspergillus species: An emerging pathogen in onychomycosis among diabetics. Indian J Endocrinol Metab.2015; 19 (6): 811–6.
[9] Merad Y, Derrar H, Belmokhtar Z, Belkacemi M. Aspergillus Genus and Its Various Human Superficial and Cutaneous Features.2021; 1–17.
[10] Chong YS, Ro BI. Cutaneous aspergillosis. Korean J Med Mycol.2002; 7 (1): 6–13.
[11] Bongomin F, Batac CR, Richardson MD, Denning DW. A Review of Onychomycosis Due to Aspergillus Species. Mycopathologia.2018; 183 (3): 485–93.
[12] 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.
[13] 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.
[14] Craddock LN, Schieke SM. Superficial Fungal Infection. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS editors. Fitzpatrick's Dermatology.9th ed. New York: McGraw Hill; 2019. pp.2925–2951.
[15] Dars S, Banwell HA, Matricciani L. The use of urea for the treatment of onychomycosis: a systematic review. J Foot Ankle Res.2019; 12: 22.
[16] Tsang CC, Hui TWS, Lee KC, Chen JHK, Ngan AHY, Tam EWT, et al. Genetic diversity of Aspergillus species isolated from onychomycosis and *Aspergillus hongkongensis* sp. nov., with implication to antifungal susceptibility testing. *Diagn Microbiol Infect Dis.*2016; 84: 125–134.