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TINEA UNGUIUM CAUSED BY TRICHOPHYTON MENTAGROPHYTES WITH PLANTAR HYPERHYDROSIS : A CASE REPORT

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Abstract

Introduction: Tinea unguium, or onychomycosis, is a common fungal infection affecting the nails, particularly prevalent among the elderly, and is primarily caused by dermatophytes like *Trichophyton mentagrophytes*. This report highlights a case of onychomycosis in a male patient with plantar hyperhidrosis, treated with a combination of itraconazole and Mentholatum ointment, aiming to improve understanding of the disease, its predisposing factors, and effective treatment approaches.

Case: A 38-year-old Batak man presented with discolored, thickened toenails, mainly affecting the fourth toe of his left foot, which had persisted for five years. Physical examination and OSI assessment identified severe tinea unguium in the fourth toe, with mild involvement in the fifth toe. Diagnostic tests including KOH analysis and dermoscopy supported the diagnosis of onychomycosis. The treatment plan involves pulse-dose itraconazole and topical application of a camphor, menthol, and essential oil ointment, with comprehensive patient education on adherence and preventive measures. Follow-up is scheduled in four weeks to monitor progress and adjust treatment as needed.

Conclusion: A male patient with plantar hyperhidrosis and tinea unguium caused by *Trichophyton mentagrophytes* was diagnosed through history, physical examination, and tests. He is undergoing combination therapy with pulse-dose itraconazole and a camphor, menthol, and essential oil regimen, showing significant clinical improvement after 4 weeks, with further follow-up planned and a prognosis considered dubius ad bonam.

Keywords: tinea unguium; onychomycosis; *Trichophyton mentagrophytes;* hyperhidrosis

INTRODUCTION

A fungal infection affecting the fingernails or toenails, known as tinea unguium or onychomycosis, can impact individuals of all ages, though it is particularly prevalent among the elderly. Despite its prevalence, nail fungus is generally not considered a severe health threat. When dermatophytes are the causative agents, the condition is specifically termed tinea unguium. Onychomycosis encompasses infections caused by dermatophytes, yeasts, and saprophytic fungi. While onychomycosis can affect both the fingernails and toenails, it is significantly more common in the toenails. Although not usually life-threatening, onychomycosis can result in serious complications, including cellulitis, sepsis, osteomyelitis, tissue damage, and nail loss.[1,2]

In a study conducted by Halvaee, dermatophytes were identified as the most prevalent etiological agents of onychomycosis, with yeast and non-dermatophytic mold onychomycosis (NDMO) following.[3] The prevalence of tinea unguium in Asia ranges from 10% to 12.1%, while in Indonesia it is between 3.5% and 4.7%.[4,5] According to patient registration data from the Skin and Gender Polyclinic at Prof. Dr. I G.N.G. Ngoerah Denpasar Hospital, Mycology Division, for the period from January 2023 to December 2023, a total of 36 cases of tinea unguium were recorded.[6] Generally, 80-90% of tinea unguium cases are attributed to dermatophytes such as *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.[7,8]

According to epidemiological, clinical, and mycological criteria, *Trichophyton mentagrophytes* is classified into two varieties: the zoophilic variety (*var. mentagrophytes*) and the anthropophilic variety (*var. interdigitale*).[9] Morphologically, the fungus is distinguished by the formation of fine-walled macroconidia and microconidia. A notable characteristic of *T. mentagrophytes* is its production of spherical micro-aleuriospores, which are typically arranged in clusters resembling a bunch of grapes.[10]

Hyperhidrosis is characterized by excessive activity of the eccrine sweat glands, occurring despite normal body temperature. This condition commonly peaks between the ages of 18 and 54. Plantar hyperhidrosis specifically refers to excessive sweating of the soles of the feet. Beyond causing discomfort, the

persistent moisture leads to skin maceration and a heightened risk of secondary skin conditions, such as fungal infections. These infections include dermatophyte-related conditions such as tinea pedis, tinea manum, tinea corporis, and tinea cruris. In individuals with both onychomycosis and hyperhidrosis, the maceration of the skin diminishes its natural defense against fungal infections, while the moist environment promotes fungal growth and proliferation.[14,15] In a study by Zheng and colleagues, 13 out of 40 patients with onychomycosis and hyperhidrosis received treatment, with 20 patients treated solely for onychomycosis and the remaining 20 treated for both onychomycosis and hyperhidrosis. Of those treated only for onychomycosis, 16 were cured, whereas all patients treated for both conditions achieved a cure.[15] Additionally, research by Wardawa and colleagues found that hyperhidrosis was present in 20.2% of patients with various infections, including bacterial, viral, fungal, and scabies infections, with fungal infections specifically accounting for 8.1%.[16]

The management of tinea unguium focuses on delivering optimal treatment based on factors such as the infection's location, potential drug interactions, and disease severity. The primary objective of therapy is to eradicate the fungal infection and restore the nail to its normal state.[13,17,18] Known therapeutic approaches include systemic antifungal medications, topical treatments, and mechanical interventions such as nail avulsion and debridement, either alone or in combination.[13] Combination therapy, utilizing both systemic and topical antifungals, generally achieves higher cure rates compared to monotherapy. This combined approach can enhance the speed of healing, reduce the likelihood of relapse, improve drug tolerance and safety, minimize drug resistance, and lower overall treatment costs.[19]

Mentholatum ointment, containing 4.8% camphor and 2.6% menthol, is commonly used as a home remedy for onychomycosis.[40] Although no published clinical trials have assessed its efficacy for treating onychomycosis, in vitro studies have demonstrated its effectiveness against dermatophytes. Menthol is known to penetrate the nail and target the fungal elements responsible for nail damage, showing specific inhibition of many fungi that cause onychomycosis.[41] In contrast, camphor has minimal antifungal properties. However, a formulation

containing 4% menthol and 2% camphor has been found to be significantly more effective in eradicating nail fungus. This enhanced efficacy is attributed to camphor's role as a penetration enhancer, facilitating better access of menthol to the fungus beneath the toenail bed.[41] Additionally, essential oils, often used as alternative treatments for dermatophytosis, possess varying degrees of antifungal activity due to their lipophilic nature.[42]

This report describes a case of tinea unguium in a male patient with plantar hyperhidrosis, caused by *Trichophyton mentagrophytes*, who was treated with a combination of itraconazole and Mentholatum ointment. The purpose of this case report is to enhance understanding of tinea unguium, its predisposing factors, and the selection of appropriate treatment strategies for affected individuals.

CASE

A 38-year-old man of Batak ethnicity, with medical record number 01601161, presented to the Skin and Gender Polyclinic at Prof. Dr. I.G.N.G. Ngoerah Hospital on February 7, 2024. He reported experiencing discolored, brittle, dull, and thickened toenails for the past five years.

From the anamnesis, the patient reported that the nails on the ring and little fingers of his left foot have exhibited discoloration for the past five years. Although the patient had observed the discoloration for an extended period, he had not sought treatment for his toenails. The discoloration is described as a brownish-yellow hue. The patient denied experiencing itching or pain. Initially, the nails became thickened, and over time, they also showed discoloration, dullness, and brittleness. Additionally, the patient noted recurring redness and itching between his ring toenails, leading to scratching and wound formation. The patient also mentioned frequent sweating of the feet. Notably, the patient's father has reported similar symptoms.

There was no prior history of similar symptoms reported. Nail growth has proceeded normally. The patient denied having a history of diabetes, hypertension, cardiovascular disease, liver or kidney disorders, and malignancies. There were no reports of weight loss, cough, or diarrhea. Neither family members

nor neighbors have experienced similar complaints. Family history of diabetes, hypertension, or any heart, liver, or kidney disorders was also denied. The patient had previously used miconazole cream for interdigitally applied issues but reported no long-term use of medications. Additionally, there was no history of using ointments or herbal treatments on the nails.

In terms of social history, the patient is currently employed as a civil servant (ASN). The patient engages in sports activities, including jogging, badminton, and gym workouts. The patient noted frequent nail trauma due to shoe friction during exercise. There was no reported history of smoking or alcohol consumption. The patient previously owned a pet dog but has not had contact with it for approximately five years; however, the patient regularly bathed the dog while it was still in their care. The patient lives alone and performs nail trimming independently at home.

On physical examination, the patient appeared to be in good general condition with intact consciousness. Vital signs were as follows: blood pressure 120/70 mmHg, pulse 82 beats per minute, respiratory rate 20 breaths per minute, and axillary temperature 36.6°C. The Visual Analog Scale (VAS) score was 0/10. The patient's weight was 75 kg, height 165 cm, and BMI 27.5 kg/m², indicating overweight. The general examination revealed a normal head and facial appearance, with no hyperemia in the conjunctiva or jaundice in the sclera observed during ocular assessment. Examination of the ears, nose, and throat showed no abnormalities. Cardiovascular examination noted regular heart sounds S1 and S2, with no murmurs or gallops. Lung examination revealed vesicular breath sounds throughout both lung fields, without the presence of rhonchi or wheezing. Abdominal examination showed normal bowel sounds, no distension, and no enlargement of the liver or spleen, with good skin turgor. Examination of the upper and lower extremities showed warmth, no edema, and strong pulsation of the dorsalis pedis artery. There was no lymphadenopathy detected.

On dermatological examination, the nail of the fourth toe on the left foot (digiti IV pedis sinistra) exhibited brownish-yellow and blackish discoloration, along with subungual hyperkeratosis with a thickness greater than 2 mm. Beau's

lines were present on this nail. The nail of the fifth toe on the left foot (digiti V pedis sinistra) showed yellowish discoloration.

The Onychomycosis Severity Index (OSI) assessment revealed severe onychomycosis in the fourth toe of the left foot (digiti IV pedis sinistra), characterized by brownish-yellow discoloration. The nail plate area involved was between 76-100%, scoring 5, with matric involvement exceeding 3/4, which scored 4. Subungual hyperkeratosis with a thickness greater than 2 mm contributed a score of 10, resulting in a total OSI score of 30. In contrast, the fifth toe on the left foot (digiti V pedis sinistra) showed yellow discoloration with only 1-10% of the nail plate area involved (score 1) and less than 1/4 of the matric involved (score 1). No subungual hyperkeratosis was present. The total OSI score for this toe was 1, indicating mild onychomycosis.

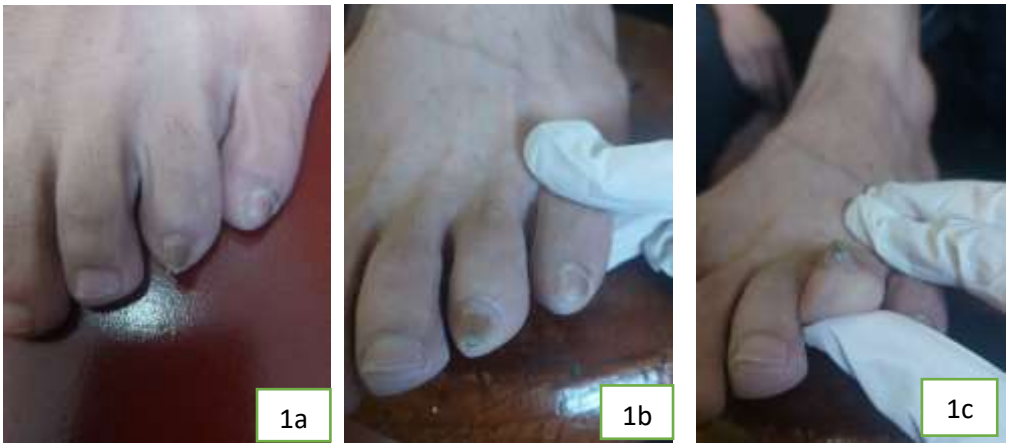

Figure 1a-c. On the fourth toe of the left foot (digiti IV pedis sinistra), examination revealed brownish-yellow and blackish discoloration, with subungual hyperkeratosis exceeding 2 mm in thickness. Beau's lines were present (see Figure 1a-1c).

The history and physical examination led to a differential diagnosis that included DLSO-type tinea unguium, fungal melanonychia, and Candida onychomycosis.

Supporting examinations included toenail scraping with 20% potassium hydroxide (KOH) and dermoscopy. The 20% KOH analysis of the toenail scrapings identified a single spore. The dermoscopic evaluation revealed brownish-yellow discoloration, subungual hyperkeratosis, longitudinal leukonychia, longitudinal striae, irregular nail termination, and yellowish streaks

(Figure 2). Additionally, nail scrapings were cultured on Sabouraud Dextrose Agar (SDA) medium, and a comprehensive blood test was conducted, including assessments of liver function, kidney function, and blood glucose levels. The complete blood count on February 7, 2024, showed leukocytes at 5.88 x 10^3/µL (normal range 4.1-11.0), neutrophils at 55.6% (normal range 47-80%), lymphocytes at 27.0% (normal range 13-40%), monocytes at 8.0% (normal range 2-11%), eosinophils at 8.5% (normal range 0-5%), and basophils at 0.9% (normal range 0-0.2%). Hemoglobin was 14.2 g/dL (normal range 12.0-16.0), hematocrit was 43.8% (normal range 36-46%), and platelets were 179 x 10^3/µL (normal range 140-440). Liver enzyme levels were SGOT 23.0 U/L (normal range <34.0) and SGPT 23.0 U/L (normal range <55). Urea was 24.4 mg/dL (normal range <48), creatinine was 1.10 mg/dL (normal range 0.72-1.25), and blood glucose was 78.7 mg/dL (normal range 70-140 mg/dL).

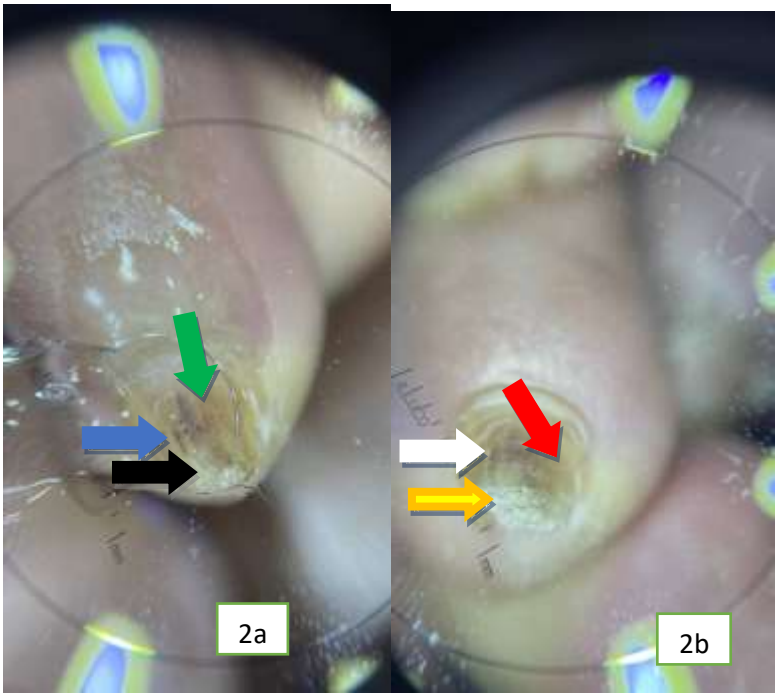

Figure 2a-b The dermoscopic examination of the digiti IV pedis dextra revealed several features: brownish-yellow dyschromia (blue arrow), subungual hyperkeratosis (yellow arrow), longitudinal leukonychia (black arrow), longitudinal striae (white arrow), irregular nail termination (green arrow), and yellowish streaks (red arrow).

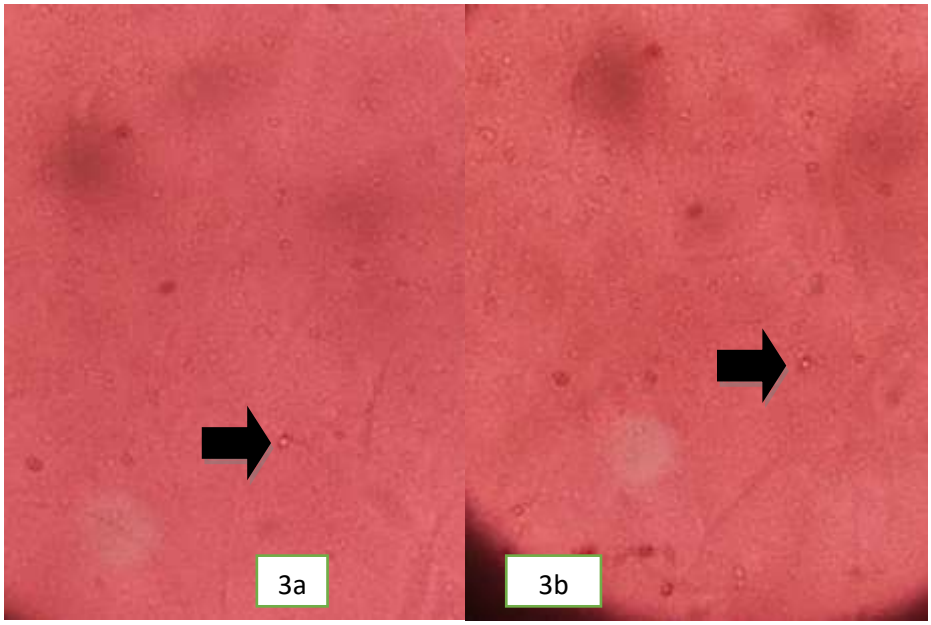

Figure 3. The 20% KOH examination of the nail scrapings revealed a single spore (black arrow).

The working diagnosis for this patient is severe tinea unguium affecting the fourth toe of the left foot (digiti IV sinistra) and mild tinea unguium affecting the fifth toe of the left foot (digiti V sinistra). The treatment plan includes itraconazole 400 mg capsules administered as a pulse dose weekly for three months and topical application of an ointment containing camphor, menthol, and essential oils every 12 hours to the toenail area. The patient received comprehensive information and education (IEC) regarding the condition, examination results, treatment duration, medication usage, the importance of adherence to treatment, and measures to avoid risk factors, such as refraining from using public baths, opting for open shoes or sandals, daily washing of socks, drying shoes daily, and ensuring feet are dry after bathing. Additionally, the patient was informed about the therapy plan, potential side effects of the medication, and reminded to return for a follow-up visit in four weeks.

FOLLOW-UP OBSERVATION I (week-4: 14th March2024)

Upon follow-up, the patient reported that the lesion had not increased in size. The yellow-brown discoloration of the nails persisted but had reportedly faded. The patient experienced no itching, redness, or swelling around the nails.

Additionally, the patient denied experiencing any nausea, vomiting, or headaches during or after the treatment.

On physical examination, the patient was in good general condition with composmentis intact consciousness. Vital signs included a blood pressure of 120/70 mmHg, a pulse rate of 82 beats per minute, a respiratory rate of 20 breaths per minute, and an axillary temperature of 36.5°C. The general status examination was within normal limits.

The dermatologic examination of the digiti IV pedis sinistra revealed brownish-yellow and blackish discoloration, along with subungual hyperkeratosis exceeding 2 mm in thickness. No abnormalities were observed on digiti V pedis sinistra. Dermoscopic evaluation showed brownish-yellow discoloration, subungual hyperkeratosis, longitudinal leukonychia, and yellowish streaks (see Figure 4d-4e).

The Onychomycosis Severity Index (OSI) assessment for digiti IV pedis sinistra, there was yellow-brownish-blackish discoloration with involvement of 26-50% of the nail plate area (score 3), matrix involvement between 1/4 and 1/2 (score 2), and subungual hyperkeratosis exceeding 2 mm (score 10). The total OSI score for this toe was 16, which indicates severe onychomycosis.


4a
4b
4c
4d
4e

Figure 4a-c. The nail of digiti IV pedis sinistra exhibited brownish-yellow and blackish discoloration, along with subungual hyperkeratosis exceeding 2 mm in thickness. Dermoscopic examination revealed brownish-yellow discoloration, subungual hyperkeratosis (yellow arrow), longitudinal leukonychia (blue arrow), and yellowish streaks (brown arrow) (**Figure 4d-4e**).

The culture support examination revealed colony growth on the seventh day (February 15, 2024). The colonies appeared white, flat with a convex center, and had a downy, cotton-like texture. The surrounding surface ranged from white to beige, while the reverse side was bright yellow (**Figure 5a-b**). Microscopic analysis showed macroconidia that were cigar-shaped or resembling beating sticks, with thin, parallel internal walls. Microconidia were spherical with smooth walls, and were accompanied by skeletal hyphae, spiral hyphae, and conidiospores (**Figure 6a-b**). These characteristics are consistent with the species *Trichophyton mentagrophytes*.

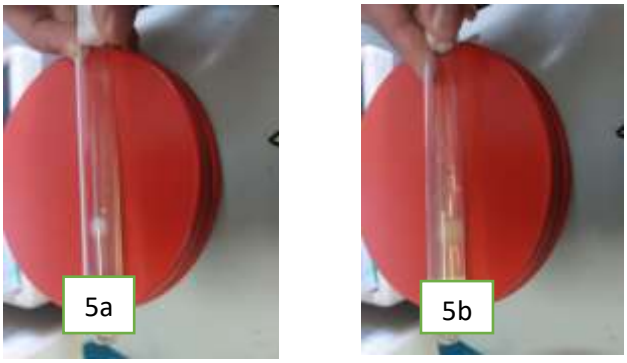

Figure 5a-b. The culture of *Trichophyton mentagrophytes* on SDA media showed colonies that were flat and white with a convex center and a cotton-like, fluffy texture (Figure 5a). The reverse side of the colonies was bright yellow (Figure 5b).

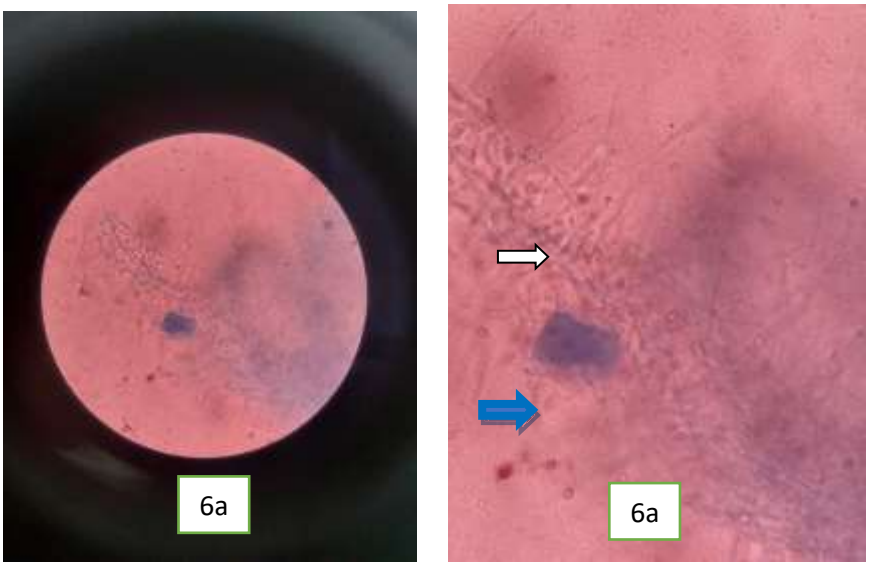

Figure 6a-b. Microscopic examination of the culture specimens of *Trichophyton mentagrophytes* revealed long hyphae with spiral-shaped circular septa (white arrows) and microconidia (blue arrows).

The working diagnosis for this patient is follow-up of severe tinea unguium on digiti IV sinistra and mild tinea unguium on digiti V sinistra, which has shown improvement. The treatment plan includes itraconazole 400 mg capsules administered as a pulse dose weekly (second dose, with a plan for a total duration of three months), along with a topical ointment containing camphor, menthol, and essential oils applied every 12 hours to the toenail area. The patient received comprehensive information and education (IEC) regarding the condition, examination results, treatment duration, proper medication usage, the importance of adherence to treatment, and strategies to avoid risk factors such as refraining from using public baths, opting for open shoes or sandals, washing socks daily, drying shoes daily, and ensuring hands and feet are dry after bathing. The patient was also informed about potential side effects of the medications and advised to return for a follow-up visit in four weeks.

DISCUSSION

Onychomycosis is a fungal infection affecting the nail unit, with dermatophyte-induced cases specifically termed tinea unguium. The broader category of onychomycosis encompasses infections caused by dermatophytes, yeasts, and saprophytic fungi. Abnormal nail conditions not resulting from fungal

infections are referred to as dystrophic nails. While onychomycosis can impact both fingernails and toenails, toenail infections are significantly more prevalent.[1] The condition is widespread globally and shows a tendency to persist and expand. The increased incidence observed among adults, children, and the elderly may be attributed to factors such as environmental conditions, demographic characteristics, lifestyle changes, and immune system suppression.[2]

This prevalent fungal infection accounts for 50% of all nail disorders and affects approximately 10% of the global population, with varying frequencies across different regions. It is most commonly observed in adults, particularly in urban areas, with a male-to-female ratio of 1.5:1. The prevalence of onychomycosis tends to increase with age, with toenails being the most frequently affected (70%). Additionally, tinea pedis is the most common accompanying condition in these patients.[2,20]

The prevalence of onychomycosis is approximately 2.6% among children under the age of 18, significantly increasing from ages 30 to 60, and reaching up to 90% in the elderly.[11,21] Additionally, about 30% of patients with fungal skin infections also experience fungal infections in their nails. Tinea unguium is typically transmitted through direct contact with an infected individual or contaminated objects such as nail clippers, footwear, swimming pool surfaces, showers, and other communal facilities, as well as through contact with infected animals. Nail abnormalities may initially present as tinea pedis or directly affect the nails.[5,11]

The most common etiological agents of tinea unguium are *Trichophyton rubrum* (71-88%) and *Trichophyton mentagrophytes* var. *interdigitale* (9-22%), with less frequent occurrences of *Trichophyton tonsurans* and *Epidermophyton floccosum*. *Trichophyton* species can infect both humans and animals. These fungi are frequently found in warm, moist environments and exhibit keratinolytic properties, which enable them to degrade keratin present in the nails, leading to nail fragility and damage.[2,4]

Dermatophytes can be transmitted from animals to humans under certain conditions, including direct contact with infected animals and their habitats.[22] Contact with infection sources is a significant risk factor.[24] Additional risk factors

for tinea unguium include advancing age, hot and humid climates, occlusive conditions, repeated trauma to the nails, hyperhidrosis, a history of dermatophyte infections in other locations, use of anti-inflammatory or immunosuppressive medications, and immunodeficiency conditions such as diabetes, obesity, autoimmune disorders, malignancies, hepatitis, renal failure, HIV infection, and lifestyle factors such as poor nail care, not wearing footwear, using public baths, and maintaining damp feet due to the use of socks, continuous closed shoes, or gloves. Patients with HIV who have a CD4 T-lymphocyte count below 400 cells/μL or impaired polymorphonuclear chemotaxis are at increased risk of onychomycosis, which tends to be more extensive and involve all fingernails.[5,7.23]

In this case, the patient is a 38-year-old male with predisposed factors including hyperhidrosis and regular exercise. Additionally, he owns a pet dog, which may contribute to the risk of fungal infection. The patient's lifestyle involves frequent physical activity and continuous use of closed footwear, contributing to a humid environment that favors fungal growth. Furthermore, he has a history of recurrent tinea pedis, which frequently resolves and reoccurs.

The nail unit lacks effective cellular immunity, making it particularly susceptible to fungal infections.[11] The pathogenesis of onychomycosis begins with fungal entry through the nail plate surface, lateral and proximal nail folds, and the hyponychium. Following initial adhesion, the fungi grow, germinate, and penetrate the nail tissue. The invasion starts from the ventral side of the nail plate, extending to the nail bed, with the fungi penetrating through the entire nail structure, predominantly within the intercellular spaces. This gradual invasion damages the nail. Damage to the stratum corneum, maceration, and a moist environment facilitate fungal entry into the epidermal layers. Dermatophytes produce several keratinolytic, proteolytic, and lipolytic enzymes that degrade nail components. Keratin hydrolysis by these enzymes aids fungal invasion, as the degradation products serve as nutrients for fungal growth. The extent of dermatophyte invasion into the stratum corneum varies and is influenced by host resistance. The low cellular immunity in the nail makes it vulnerable to infection. Infections are typically chronic due to reduced expression of Major Histocompatibility Complex (MHC) I, dysfunction of Langerhans cells and

macrophages, which diminishes their antigen-presenting capability, and decreased activity of Natural Killer cells around the nail folds, nail plate, and nail matrix.[11,25,26]

Onychomycosis presents in various clinical subtypes, including distal and lateral subungual onychomycosis (DLSO), proximal subungual onychomycosis (PSO), superficial onychomycosis (SO), endonyx onychomycosis (EO), total dystrophic onychomycosis (TDO), and mixed onychomycosis (MO). DLSO is the most frequently observed type in immunocompetent individuals. It is characterized by fungal invasion originating from the hyponychium and distal nail base, extending through the nail plate to the proximal nail folds. Clinically, this results in thickened, opaque distal nails, accompanied by subungual hyperkeratosis, onycholysis, and a yellow-brown discoloration. Progressive subungual hyperkeratosis leads to nail dystrophy. PSO starts at the proximal nail folds and spreads distally, presenting as opaque white patches on the proximal nail plate, onycholysis, and progressive destruction affecting the entire nail. SO involves a superficial infection of the outer nail plate, with fungi entering from beneath the proximal nail folds or through the nail plate itself. EO is marked by extensive invasion of the nail plate without involvement of the nail bed, with fungal hyphae penetrating directly into the distal nail plate. TDO can either be a final stage of any onychomycosis type (secondary) or occur primarily in individuals with chronic mucocutaneous candidiasis or other immunocompromised states.[27-29]

In this case, the patient reported a history of changes to the toenail on the left fourth digit over the past five years, initially noting thickening at the nail tip, which progressively developed into discoloration, dullness, and brittleness. The clinical presentation is consistent with distal lateral subungual onychomycosis (DLSO).

Differential diagnosis for the patient includes fungal melanonychia (MF). MF is a rare nail disorder characterized by dark brown to black pigmentation resulting from fungal infection of the nail. It is predominantly caused by dematiaceous fungi, though yeasts and non-dermatophyte molds can also be implicated. Diagnosing MF can be challenging due to its clinical similarity to

melanonychia from other causes, such as melanocytic nevi and subungual melanoma. Certain fungal species are capable of synthesizing melanin, which differs from human melanin synthesized from tyrosine; fungal melanin is produced via the pentaketide pathway. This melanin acts as a protective barrier for the fungi against environmental stresses such as UV radiation, temperature extremes, and host immune responses. Additionally, melanin-synthesizing fungi exhibit greater resistance to UV radiation, X-rays, and extreme temperatures compared to other fungi. Among the fungi commonly isolated in cases of MF are *Trichophyton rubrum*, a non-dematiceous dermatophyte, and *Scytalidium dimidiatum*, a dematiaceous fungus.[45] Nails affected by MF typically present with brown to black discoloration, sometimes showing dystrophy and associated with subungual hyperkeratosis. Periungual inflammation is often observed. Fungal culture remains a crucial method for identifying the causative organism and should be performed by experienced laboratories.[46] Dermoscopic features such as triangular patterns, subungual hyperkeratosis, and white or yellow streaks are characteristic of MF, with white or yellow streaks and reverse triangular patterns being particularly indicative.[45]

The patient was also evaluated for a differential diagnosis of Candida onychomycosis. Candida spp.-induced onychomycosis, referred to as Candida onychomycosis, has been reported with a prevalence of 47.86% among onychomycosis patients in studies conducted in Saudi Arabia and Iran. This condition is more prevalent among individuals with risk factors such as moisture exposure, water-related occupations, immunodeficiency, endocrine disorders, smoking, malnutrition, and peripheral vascular disease. Candida onychomycosis predominantly affects the fingernails rather than the toenails.[23] Clinically, Candida onychomycosis frequently results in chronic paronychia, characterized by redness, swelling, and pain, which presents as a bulbous or drumstick appearance in the periungual area. The loss of the nail cuticle and tenderness of the nail plate are common features associated with this condition. Unlike dermatophytes, Candida affects the nail plate only after involving the surrounding soft tissue. Following involvement of the nail matrix, Beau’s lines and dystrophy may appear on the nail plate. High moisture levels and continuous exposure to

water-related activities are significant risk factors for Candida infection.[2,6] It is important to note that the presence of Candida blastospores in KOH preparations from nail scrapings or histopathological examinations is not unusual, given Candida's status as a common skin commensal. However, the presence of pseudohyphae identified through KOH or PAS staining is a strong indicator of invasive Candida infection.[30] The patient reported a long-standing yellow-brown to black discoloration of the nails, associated with high moisture levels due to consistent use of occlusive footwear during work and exercise, compounded by hyperhidrosis causing damp feet. Although pseudohyphae were not detected in the KOH examination, fungal culture remains the most specific test for identifying the causative fungal agent.

Dermoscopy can be a valuable diagnostic tool; however, it should not be relied upon as the sole criterion for diagnosis based on the results obtained. Dermoscopic examination of onychomycosis reveals features such as short spikes, longitudinal striae, and an aurora borealis appearance. These characteristics are significantly correlated with positive mycological test results, with a sensitivity of 90.4% for onychomycosis.[31] In this case, the dermoscopic findings include yellow-brown discoloration, subungual hyperkeratosis, longitudinal leukonychia, longitudinal striae, irregular terminations, and yellowish streaks. These dermoscopic features are also observed in non-dermatophyte onychomycosis and malanonychia, indicating that a differential diagnosis of malanonychia cannot be excluded.

The diagnosis of tinea unguium is established through anamnesis, physical examination, KOH testing, and fungal culture. In tinea unguium, microscopic examination of nail scrapings with 20% KOH solution reveals septate hyphae with walls consisting of two parallel, transparent lines (double contour), branching structures, and occasionally, spore chains at the hyphal tips.[11] In this case, the KOH examination identified single spores but did not reveal pseudomycelia, thus highlighting the necessity of fungal culture to accurately determine the causative agent of the infection.

Fungal culture is the most specific diagnostic method for onychomycosis.[4] It allows for the identification of specific pathogen subtypes. Following the

collection of debris from the nail plate, subungual specimens are cultured on Sabouraud dextrose agar (SDA) at 26–30°C for up to one month. To inhibit bacterial contamination, SDA is supplemented with chloramphenicol and gentamicin. Laboratory procedures often involve culturing subungual specimens on SDA both with and without cycloheximide, which suppresses the growth of non-dermatophyte molds (NDM). Multiple cultures may be necessary to diagnose NDM onychomycosis, as NDMs frequently contaminate skin surfaces. Fungal culture exhibits a specificity of 99% and a sensitivity of 56% (ranging from 29% to 82%) according to recent meta-analysis studies.[20,21]

The morphology of *Trichophyton rubrum* is characterized by white colonies with a central raised area and a maroon edge, while the reverse side of the colony also exhibits a maroon hue. Microscopically, *T. rubrum* is identified by tear-shaped microconidia and pencil-shaped macroconidia. In contrast, *Trichophyton mentagrophytes* forms white colonies that are flat with a central convexity and a cottony texture; the surrounding area is white to cream, and the reverse side is bright yellow. Microscopic examination reveals round microconidia, resembling grape clusters, located on terminal branches and scattered along hyphal edges. Thin-walled, cigar-shaped macroconidia are infrequent, and spiral-shaped hyphae may be present. *Epidermophyton floccosum* produces colonies with a woolly appearance and central yellow-brown folds. Microscopically, it lacks microconidia but features club-shaped macroconidia with both thin and thick walls. *Candida* species generate white to yellowish colonies that are smooth and creamy, and microscopically, they display blastospores and pseudohyphae.[4] In this case, the culture findings are consistent with *Trichophyton mentagrophytes*.

The genus Trichophyton is notably complex.[23] comprising at least 15 recognized species. *T. mentagrophytes* exhibits both anthropophilic and zoophilic characteristics. Specifically, *T. mentagrophytes* var. *interdigitale* is anthropophilic and frequently associated with onychomycosis and tinea pedis. In contrast, *T. mentagrophytes* var. *mentagrophytes* is zoophilic, primarily transmitted from animals to humans through direct contact or indirectly via infected animal fur that may adhere to clothing or contaminate living environments such as bedding and

food. Major sources of transmission include dogs, cats, cattle, horses, and mice.[22,23] *T. mentagrophytes* var. *interdigitale* is more commonly linked to tinea pedis and tinea unguium, while T. mentagrophytes var. mentagrophytes more often causes tinea corporis, tinea faciei, tinea cruris, and tinea capitis, with tinea unguium being less frequent.[24] To differentiate between these two varieties, *T. mentagrophytes* var. *mentagrophytes* cultures typically present as flat, granular colonies with irregular edges that grow radially and are cream to dark brown in color, with the reverse side ranging from brown to reddish-brown. Microscopic examination reveals scattered microconidia along the periphery of the mycelium, though less frequently than in *T. mentagrophytes* var. *interdigitale*, and macroconidia that appear similar. Spiral hyphae are more commonly observed in *T. mentagrophytes* var. *mentagrophytes*.[22-24] In this case, the infection was identified as *Trichophyton mentagrophytes*, suggesting that the suspected source of transmission was the patient's pet.

The Onychomycosis Severity Index (OSI) is a scoring system used to evaluate the severity of onychomycosis, guide treatment decisions, and monitor therapy. The OSI is calculated by assessing the percentage of the nail plate affected, involvement of the proximal area up to the nail matrix, the thickness of subungual hyperkeratosis, and the presence of dermatophyte granulomas. Affected nail plate area is scored as follows: 1 point for 1-10%, 2 points for 11-25%, 3 points for 26-50%, 4 points for 51-75%, and 5 points for 76-100%. This score is then multiplied by the degree of proximal involvement: 1 point if less than ¼ of the nail matrix is affected, 2 points if ¼ to ½ is involved, 3 points if more than ½ to ¾ is affected, 4 points if over ¾ is involved, and 5 points if the nail matrix is affected. The result is summed and an additional 10 points is added if longitudinal striae (dermatophyte granulomas) or subungual hyperkeratosis greater than 2 mm in thickness are present. The interpretation of the OSI score categorizes onychomycosis as mild (scores 1-5), moderate (scores 6-15), or severe (scores 16-35).[25,26]

In the initial evaluation, the OSI for the left fourth toe revealed yellow-brown discoloration with 76-100% of the nail plate affected (score 5), proximal involvement greater than ¾ (score 4), and subungual hyperkeratosis exceeding 2

mm in thickness (score 10), resulting in a total OSI score of 30, indicative of severe onychomycosis. Conversely, for the left and right fifth toes, yellow discoloration was observed with only 1-10% of the nail plate involved (score 1) and less than ¼ of the nail matrix affected (score 1). No subungual hyperkeratosis was noted, leading to a total OSI score of 1 for the left fifth toe, reflecting mild onychomycosis. After a follow-up period of 4 weeks, the OSI score for the left fourth toe decreased to 16, and the score for the left fifth toe reduced to 0.

Predisposing factors for onychomycosis include fungal infections in other body areas (particularly tinea pedis), chronic paronychia, previous onychomycosis, the use of occlusive and tight footwear, hyperhidrosis, athletic activities or fitness regimes, nail trauma, poor nail care, exposure to public swimming pools and communal baths, cohabitation with individuals who have fungal infections, poor overall health, genetic factors, immunodeficiency (notably AIDS and transplant patients), diabetes mellitus, obesity, Down syndrome, psoriasis, smoking, peripheral vascular disease, venous insufficiency, hallux valgus, and asymmetric gait nail unit syndrome.[5,11]

Hyperhidrosis generally affects approximately 3% of the population, though this figure may not account for unreported cases due to patient embarrassment.[27] This condition typically manifests in areas with a high density of eccrine glands, such as the plantar surfaces, palms, and craniofacial regions, as well as in areas with apocrine glands, such as the axilla. Women are slightly more likely to experience axillary hyperhidrosis, but significant gender-based prevalence differences have not been identified. Plantar hyperhidrosis usually begins between the ages of 0 and 19, with nearly 56% of cases occurring between 0 and 11 years of age. It is suspected that hyperhidrosis may resolve spontaneously over time, as its prevalence decreases among the elderly. While hyperhidrosis is a common condition with diverse etiologies, focal hyperhidrosis, such as when it affects only the plantar surfaces of the feet, is often idiopathic. However, other potential causes of focal hyperhidrosis include malignancies and genetic conditions such as epidermolysis bullosa, congenital pachyonychia, palmoplantar keratoderma syndrome, or autonomic dysfunction of the eccrine glands.[15,28]

Plantar hyperhidrosis is typically classified as primary and idiopathic, though hyperhidrosis can be categorized into primary and secondary forms. Primary hyperhidrosis is often an idiopathic increase in sympathetic nervous system activity, whereas secondary hyperhidrosis is usually attributed to medications or underlying conditions.[28] Evidence suggests that primary hyperhidrosis may be an autosomal dominant trait with variable penetrance. A study involving 410 patients in Japan found that 36% had a family history of palmoplantar hyperhidrosis, with the most common pattern being parent-to-child transmission (58%), and 13% of patients reported the condition spanning three generations. According to Lear and colleagues, nearly 44% of individuals reported a familial connection to hyperhidrosis. In a study by Lima and associates involving 447 medical students, 45% reported a family history of the condition.[30] Primary hyperhidrosis typically presents bilaterally and symmetrically, affecting the axillae, palms, soles, and craniofacial regions, and is associated with increased skin infections. Specifically, 25% of patients experience hyperhidrosis in both palms and soles; 15.5% are affected in the soles alone; and 11% report involvement of the axillae, palms, and soles.[15]

The risk of skin infections is elevated in areas affected by hyperhidrosis. This condition significantly increases the likelihood of fungal infections, particularly dermatophyte infections on the skin, such as tinea pedis, tinea manuum, tinea corporis, and tinea cruris.[15,32] In patients with both onychomycosis and hyperhidrosis, skin maceration diminishes the skin’s defenses against fungal pathogens, creating a moist environment conducive to fungal growth and proliferation. Beyond fungal infections, individuals with hyperhidrosis are also at greater risk for bacterial and viral infections.[15,33]

The diagnosis of primary hyperhidrosis is confirmed if at least two diagnostic criteria are met and persist for over six months. These criteria include: 1) the hyperhidrosis is bilateral and symmetrical, 2) it causes significant interference with daily activities, 3) the onset occurs before the age of 25, 4) there is a family history of similar complaints, 5) hyperhidrosis diminishes or resolves during sleep, and 6) there is at least one episode of excessive sweating per week. The starch-iodine test is a simple and cost-effective method used to detect

sweating, identify affected areas, and assess the extent of excessive sweat production. This technique is particularly useful for mapping sweat focal points before and after treatments, such as botulinum toxin injections or surgical interventions. While the test does not measure the severity of hyperhidrosis, it helps in distinguishing varying intensities of sweating.[31]

A notable predisposing factor in this patient is hyperhidrosis, characterized by a persistent issue of excessive moisture on the palms and soles, which does not occur during sleep. Additionally, the patient's father exhibits similar symptoms. Two diagnostic criteria for hyperhidrosis have been met in this case. The starch-iodine test revealed a deep brownish-black discoloration, indicative of pronounced sweating. The patient's hyperhidrosis is triggered by physical activity and anxiety. Beyond fungal nail infections, the patient has a history of recurrent fungal infections between the toes, which improved with treatment using miconazole.

Fungal eradication is a critical aspect of onychomycosis treatment. The goal of therapy is to achieve both clinical and mycological resolution. Mycological cure is indicated by negative results in both KOH microscopic examination and fungal culture. Clinical cure is defined as the nail appearing entirely normal, with 80-100% of the nail being healthy and residual clinical symptoms of onychomycosis affecting less than 10% of the nail.[34]

Therapeutic choices for onychomycosis are influenced by various factors including the severity of the infection, the causative organism, concurrent medical conditions, and medication costs.[34] The chemical composition of the nail presents a significant barrier to drug absorption, with poor diffusion compared to skin, and the slow growth of toenails necessitates extended topical treatment, often for 12 months or more, until healthy nail regrowth occurs. Consequently, oral therapy has become the preferred treatment due to its accessibility and effectiveness.[7] Topical antifungal monotherapy is generally effective only for early-stage onychomycosis (excluding transverse or striate infections) where less than 80% of the nail plate is involved, or when there is no involvement of the lunula, or if systemic antifungals are contraindicated.[35] Systemic antifungal therapy is employed in cases where there is involvement of the nail matrix or when a higher and faster cure rate is desired. Topical antifungal therapy may be used for distal nail involvement, white superficial

onychomycosis, or when systemic treatment is contraindicated.[4] Combining oral and topical antifungal therapies enhances penetration into infected tissues, as each treatment alone does not achieve effective concentrations. Oral therapy reaches the nail bed quickly, while topical therapy effectively penetrates the nail plate and its lateral edges but not deeper layers. Thus, combination therapy ensures bidirectional penetration of the nail plate with topical agents and the nail bed with oral medications, reducing the risk of reinfection. Evidence shows that combination therapy with both oral and topical antifungals significantly improves mycological and clinical outcomes, shortens treatment duration, and minimizes systemic side effects.[35]

In this case, systemic antifungal therapy was prescribed due to the involvement of over 50% of the nail surface and the absence of contraindications for oral antifungal agents. This approach was complemented with topical treatment to reduce side effects, enhance patient adherence to the medication regimen, and optimize treatment cost-effectiveness.

Oral antifungal agents commonly used for onychomycosis treatment include itraconazole, terbinafine, fluconazole, griseofulvin, and ketoconazole. Among these, itraconazole and terbinafine are considered the most effective systemic treatments for onychomycosis due to their ability to establish a reservoir in the nails.[35]

Itraconazole is effective against dermatophytes, yeasts, and molds, with a Minimum Inhibitory Concentration (MIC) ten times higher than that of terbinafine. Generally, itraconazole acts as a fungistatic agent, but it can exhibit fungicidal properties at concentrations up to ten times the MIC. Its mechanism of action is similar to other azole derivatives, inhibiting the cytochrome P450 enzyme system that mediates the synthesis of ergosterol, a critical component of fungal cell walls. Optimal absorption of itraconazole occurs when taken with food and in acidic pH. It is lipophilic and metabolized in the liver by the cytochrome P450 3A4 system, which can lead to interactions with other drugs metabolized through this pathway. Standard dosing includes 200 mg daily for 12 weeks in a continuous regimen, or 400 mg daily in a pulse regimen of one week per month. For fingernail onychomycosis, the pulse regimen is recommended for two periods,

while for toenail infections, three periods are advised. Like terbinafine, itraconazole penetrates the nails rapidly, with detectable levels one week after initiation and continuing for 6-9 months post-treatment. Common side effects include headache and gastrointestinal disturbances, with a lower incidence when using the pulse regimen. Liver function abnormalities occur in 1.9% of patients on pulse therapy and 3% on continuous therapy, with hepatitis being more common in continuous therapy after about four weeks. Monitoring liver function is recommended for patients with pre-existing liver conditions undergoing extended therapy. Itraconazole is contraindicated in patients with congestive heart disease due to its negative inotropic effects and can prolong the QT interval, especially when used in combination with other QT-prolonging medications.[35,36]

Current topical treatments for onychomycosis focus on formulations containing agents such as amorolfine, ciclopirox, tioconazole, efinaconazole, and tavaborole. However, improvement is typically observed in less than 30% of cases, with total cure rates falling below 20%. Consequently, alternative approaches, including chemical and physical strategies, have been explored to overcome physiological barriers and enhance drug delivery.[37] Chemically, treatments aim to disrupt nail keratin using disulfide-reducing agents (such as sodium sulfite and dithiothreitol) and keratolytic agents (such as urea, lactic acid, and salicylic acid) to facilitate drug penetration. Physically, methods include nail plate abrasion, microporation, surface etching, iontophoresis, laser treatment, photodynamic therapy (PDT), and ultraviolet radiation.[37,38]

Camphor, menthol, and essential oils exhibit comparable effectiveness to 8% ciclopirox nail lacquer, with studies reporting improved outcomes in patients with positive cultures for *Trichophyton mentagrophytes* and *Candida parapsilosis* compared to other organisms. The specific mechanisms of essential oils (EOs) remain unclear; however, EOs are known to disrupt fungal cell walls and cytoplasmic membranes. This disruption alters membrane permeability, which can impact electrolyte balance and lead to cellular content loss. Additionally, EOs affect mitochondrial membranes by altering their polarity, influencing proton flow, and impairing ATP production.[43]

A study found that daily use of camphor, menthol, and essential oils for 48 weeks resulted in a mycological cure rate of 27.8%. Clinical cure rates were reported to be between 55.6% and 83%, with a total cure rate of 22%. Additionally, no adverse effects were reported with this treatment regimen.[44]

The most critical factors influencing the prognosis of onychomycosis include patient characteristics and comorbid conditions. Outcomes are generally poorer in individuals over 60 years of age, those with early onset of the disease, and patients with more than three infected nails.[39]

In this case, the patient is undergoing pulse dosing of itraconazole, 400 mg daily for one week each month, and is applying a combination of camphor, menthol, and essential oils to the toenails every 12 hours. The patient has completed the first pulse dose and is continuing with the planned regimen of up to three pulse doses. Treatment outcomes are monitored through clinical and mycological improvements. Although the precipitating factors of hyperhidrosis are not being addressed with pharmacological therapy, the patient is managing these triggers, such as physical activity and anxiety, by avoidance. No factors contributing to poor treatment outcomes have been identified, leading to a presumed favorable prognosis for this case.

CONCLUSION

A case of tinea unguium was reported in a male patient with plantar hyperhidrosis caused by *Trichophyton mentagrophytes*. The diagnosis was established through patient history, physical examination, and supportive tests. The patient is receiving a combination therapy: itraconazole 400 mg daily in pulse doses planned for three cycles, and a regimen of camphor, menthol, and essential oils applied every 12 hours, intended for 48 weeks. After 4 weeks of treatment, significant clinical improvement has been observed, and further follow-up is required. The prognosis for the patient is considered dubius ad bonam.

REFERENCES

1. Bodman, Myron A. Syed, Hasnain A. Krishnamurthy karthik. Onychomycosis. StatPearls. National Center for Biotechnology Information. 2024
2. Asz-Sigall D, Tosti A, Arenas R. Tinea Unguium: Diagnosis and Treatment in Practice. Mycopathologia. 2017 Feb;182(1-2):95-100
3. Razavyoon, T. Hashemi, S. jamal. et al. The epidemiology and etiology of onychomycosis in 2 laboratory centers affiliated to Tehran university of medical sciences during 2019-2020. Iranian Journal Microbiology. Volume 14 Number 2 (April 2022(268-275
4. Craddock LN, Schieke M. *Superficial Fungal Infection*. Dalam: *Goldsmith LA*, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, eds. *Fitzpatrick's Dermatology In General Medicine.* Edisi 9. *New York: McGraw Hill*. 2019:h.2926-40.
5. Bramono K. Onikomikosis. Dalam: Bramono K, Suyoso S, Indriatni W, Ramali LM, WIdaty S, Ervianti E, editor. Dermatomikosis Superfisialis Pedoman untuk Dokter dan Mahasiswa Kedokteran. Edisi 2. Jakarta: Badan Penerbit FKUI;2013.p.86-99.
6. Anonim Registrasi Rawat Jalan Poliklinik Kulit dan Kelamin Subdivisi Mikologi RSUP Prof. Dr. I G.N.G. Ngoerah Denpasar. Januari 2023-Desember 2023.
7. Gupta AK, Stec N. *Recent advances in therapies for onychomycosis and its management*. F1000Res. 2019 Jun 25;8:F1000 Faculty Rev-968.
8. Fernández J, Del Valle Fernández I, Villar CJ, Lombó F. *Combined laser and ozone therapy for onychomycosis in an in vitro and ex vivo model*. PLoS One. 2021 Jun 30;16(6):e0253979.
9. Dhib I, Khammari I, Yaacoub A, et al. Relationship Between Phenotypic and Genotypic Characteristics of Trichophyton mentagrophytes Strains Isolated from Patients with Dermatophytosis. springer link. volume 182, pages 487–493, (2017)
10. Frias-De-Leon. et al. Molecular identification of isolates of the Trichophyton mentagrophytes complex.Int J Med Sci. 2020; 17(1): 45–52
11. Leung AKC, Lam JM, Leong KF, Hon KL, Barankin B, Leung AAM, Wong AHC. *Onychomycosis: An Updated Review. Recent Pat Inflamm Allergy Drug Discov*. 2020;14(1):32-45.
12. Perea S. Ramos Maria J. Garau M. et al. Prevalence and Risk Factors of Tinea Unguium and Tinea Pedis in the General Population in Spain. JOURNAL OF CLINICAL MICROBIOLOGY , Sept. 2000, p. 3226–3230
13. High WA, Fitzpatrick JE. Topikal antifungal agents. Dalam: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, eds. *Fitzpatrick's Dermatology In General Medicine*. Edisi 9. New York: McGraw Hill. 2019:h.2677-84.

14. Streker, M. Reuther, T. et al. Hyperhidrosis plantaris – a randomized, half-side trial for efficacy and safety of an antiperspirant containing different concentrations of aluminium chloride.JDDG; 2012 • 10:115–119
15. Vlahovic, C. Tracey. Plantar Hyperhidrosis, an overview. Clin Podiatr Med Surg - (2016)
16. Wadhawa, S. Agrawal, S. Chaudhary, M. Sharma, S. Hyperhidrosis Prevalence: A Disease Underreported by Patients and Underdiagnosed by Physicians. 2019 Indian Dermatology Online Journal.
17. Jaraiza-Santinabez J. *Onychomycosis in the Elderly*. A 2-year Retrospective Study of 138 Cases. *Revista Medica del Hospital General de Mexico*. 2016; 79(1): 5-10.
18. Lipner SR, Scher RK. *Onychomycosis: clinical overview and diagnosis*. *Journal of the American Academy of Dermatology*. 2019 Apr 1;80(4):835-51.
19. Jaraiza-Santinabez J. *Onychomycosis in the Elderly*. A 2-year Retrospective Study of 138 Cases. *Revista Medica del Hospital General de Mexico*. 2016; 79(1): 5-10.
20. Lim Sophie s, Ohn jungyoon, Mun Jo-Ho. Diagnosis of Onychomycosis: From Conventional Techniques and Dermoscopy to Artificial Intelligence. Frontiers in Medicine. April 2021 Volume 8
21. Ghannoum M, Mukherjee P, Isham N, Markinson B, Rosso JD, Leal L. Examining the importance of laboratory and diagnostic testing when treating and diagnosing onychomycosis. Int J Dermatol. (2018) 57:131–8. doi: 10.1111/ijd.13690
22. Ramaraj V. et al. Molecular strain typing of Trichophyton mentagrophytes (T. mentagrophytes var. interdigitale) using non-transcribed spacer region as a molecular marker. Indian J Med Res 146, November 2017, pp 636-641
23. Liu D. Coloe S, Baird R, Pedersen J. PCR identification of Trichophyton men tagroph ytes var. interdigitale and T. mentagrophytes var. mentagrophytes dermatophytes with a random primer. J. Med. Microbiol. -Vol. 46 (1997), 1043-1046
24. Chatterjee M. Datta D. Trichophyton: Changing Nomenclature and Practical Implications. 2023 Indian Journal of Dermatology | Published by Wolters Kluwer – Medknow
25. Hare AQ, Rich P. *Grading Onychomycosis*. *Onychomycosis: Diagnosis and Effective Management.* 2018;1:41-45.
26. Carney C, Tosti A, Daniel R, Scher R, Rich P, DeCoster J, Elewski B. *A new classification system for grading the severity of onychomycosis: Onychomycosis Severity Index. Arch Dermatol*. 2011 Nov;147(11):1277-82.
27. Streker M, Tilmann R, Hagen L, et al. Hyperhidrosis plantaris: a randomized, half-side trial for efficacy and safety of an antiperspirant containing different concentrations of aluminum chloride. J Dtsch Dermatol Ges 2012;10:115–9.

28. Walling HW. Clinical differentiation of primary from secondary hyperhidrosis. J Am Acad Dermatol 2011;64(4):690–5.
29. Kurta AO, Glaser DA. Hyperhidrosis and Anhidrosis. In: Kang S, Amagai M, Bruckner A, et al., eds. *Fitzpatrick's Dermatology*. 9th ed. Mc Graw-Hill; 2019:1459-1468
30. Lima SO, Araga˜o JF, Machado Neto J, et al. Research of primary hyperhidrosis in students of medicine of the State of Sergipe, Brazil. An Bras Dermatol 2015;90(5): 661–5.
31. Nanwrocky S. Diagnosis and qualitative identification of hyperhidrosis. Shanghai Chest 2019;3:35 | http://dx.doi.org/10.21037/shc.2
32. Walling HW. Primary hyperhidrosis increases the risk of cutaneous infection: a case-control study of 387 patients. J Am Acad Dermatol 2009;61(2):242–6.
33. Zheng Y, Yanqing W, Chen H, et al. Analysis of the factors influencing the therapeutic effects of onychomycosis. J Tongji Med Univ 2001;21(3):259–62.
34. lipner S.R. Pharmacotherapy for onychomycosis: new and emerging treatments. 2019 Informa UK Limited, trading as Taylor & Francis Group
35. Khamidah N. Ervianti E.Combination Antifungal Therapy for Onychomycosis.Indonesian Journal of Tropical and Infectious Disease, Vol. 7 No. 1 January–April 2018: 15–20
36. Nenoff P, Krüger C, Paasch U, Ginter-Hanselmayer G. Mycology - an update Part 3: Dermatomycoses: topical and systemic therapy. J Dtsch Dermatol Ges. 2015 May;13(5):387–410; quiz 411
37. Angelo T. et al. Chemical and physical strategies in onychomycosis topical treatment: A review. Medical Mycology, 2017, 55, 461–475
38. Borgheti-Cardoso LN, ˆAngelo T, Gelfuso GM et al. Topical and transdermal delivery of drug-loaded nano/microsystems with application of physical enhancement techniques. Curr Drug Targets. 2015; [Epub ahead of print]
39. Widaty S, Miranda E, Bramono K, Menaldi SL, Marissa M, Oktarina C, Surya D, Kusumawardhani HT. Prognostic factors influencing the treatment outcome of onychomycosis Candida. *Mycoses*. 2020;63(1):71-7.
40. Cappleman S. Effects Of Mentholatum On Onychomycosis Of The Toenail. MSN Research Projects. 132. 2023
41. Derby R. MD. et al. Novel Treatment of Onychomycosis using Over-the-Counter Mentholated Ointment: A Clinical Case Series. J Am Board Fam Med: first published as 10.3122/jabfm.2011.01.100124 on 5 January 2011
42. Baptista EB. et al. Chemical composition and antifungal activity of essential oil from Eucalyptus smithii against dermatophytes. Revista da Sociedade Brasileira de Medicina Tropical 48(6):746-752, Nov-Dec, 2015
43. Gupta P, Pruthi V, Poluri MK. Mechanistic Insights into Candida biofilm eradication potential of eucalyptol. Department of Biotechnology, Indian Institure of Technology Roorkee. India. 2019

44. Nickles A.M. et al. Complementary and Alternative Therapies for Onychomycosis: A Systematic Review of the Clinical Evidence.2022 S. Karger AG, Basel
45. Kim HJ, et al. Clinical and Dermoscopic Features of Fungal Melanonychia: Differentiating from Subungual Melanoma. Ann Dermatol Vol. 32, No. 6, 2020
46. Finch J, MD. et al. Fungal melanonychia. J AM ACAD DERMATOL VOLUME 66, NUMBER 5. 2011