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A DETAILED REVIEW ON THE ONYCHOMYCOSIS DISEASE

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ABSTRACT

Onychomycosis is type of fungal infection which affects nails, caused by various fungi including dermatophytes, non-dermatophytes Mold and Yeasts. Primary dermatophyte responsible for this infection are trichophyton mentagrophytes and Trichophyton rubrum, Non-dermatophytes Molds Like aspergillus and fusarium, and yeast such as candida alibicans, can also cause Onychomycosis. Diagnosis involves laboratory tests like nail clipping and fungal cultures. Treatment options include photodynamic treatment, laser therapy, and oral and antifungal medications. Novel antifungal agent and treatment methods, such as posaconazole and albaconazole, are showing promise. Additionally, research is ongoing for treatment like synthetic antifungal peptides, non-thermal plasma, propolis, and ultrasound recurrence. These intricate microbial communities cling to the nail and are resistant to therapy. Children can contract the fungus through existing nail abnormalities or environmental contamination. Dry-type plantar tinea pedis is commonly present in this case. Overall, Onychomycosis remains a challenging condition to treat, and further research is needed to develop more effective and safer treatments.

KEYWORDS: Onychomycosis, Etiology, Pathogenesis, Epidemiology, Clinical Features, Diagnosis & Diagnostic Studies, Complications, Treatment, Current & Future Development, Etc.

INTRODUCTION

Combining the terms "Onyx", which means nail, with "Mykes", which means, fungus, the name "Onychomycosis" has Greek roots. This condition is most common nail disorder, accounting for at least 50% of all nail diseases.[1] To ensure effective treatment, laboratory

confirmation of Onychomycosis is recommended before initiating therapy, as it provides a cost-effective approach.[2] Onychomycosis affects adults and children's, causing various nail problems. Common symptoms include nail discoloration, thickening and separation from nail bed. Others signs are nail splitting and destruction. Onychomycosis is primarily caused by dermatophytes, specifically trichophyton rubrum & trichophyton mentagrophytes. But non-dermatophyte Molds like aspergillus and Sporacariopsis brevicaulis can also cause the infection. There may also be involvement from other Molds, including Alternaria, Fusarium, Accomania, and neoscytalidium. 10-15% of cases of Onychomycosis Worldwide are caused by non-dermatophyte Molds.[3] Although nail fungal infection can also be caused by yeasts, such as candida albicans and candida parapsilosis, these infections usually affect people with diabetes or weakened immune systems. Childhood Onychomycosis is uncommon, affecting approximately 0.5-2.6% of children's. Distal subungual Onychomycosis is most prevalent type, toenails are more commonly impacted than fingernails. Ailment manifests similarly to adult cases. Children typically contract fungus through existing nail abnormalities or indirect exposure to contaminated environments, often via a parent.[4] In cases involving children, a genetic predisposition to fungal infection of the nails and soles may also be involved. To ensure effective treatment, a laboratory diagnosis is necessary to confirm Onychomycosis, as its symptom can be similar to other nail conditions. Direct microscopy is insufficient, so fungal culture is required to identify the specific fungus. Treating fungal nail infection can be challenging, and they rarely clear up without medication oral antifungal drugs prescribed by a doctor are usually the best course of therapy.[5,55]

Half of all consultations for nail disorders are related to Onychomycosis, which is the primary cause of nail infections. Research shows that this condition is more common in men and tends to increase with age in both men & women.[6] 10% of people worldwide suffer from Onychomycosis, a common fungal nail condition. Obesity, diabetes, a poor circulation are some of the conditions that raise the risk of Onychomycosis. Symptoms include thickened nails, discoloration and debris buildup. Diagnosis involves laboratory tests, Including nail clipping and fungal cultures. Treatment options include laser treatment, oral and tropical antifungals, and novel drugs that show promise. Onychomycosis is still difficult to treat, though, more research is required to provide safer and more effective therapies.[7] Moreover, dry-type plantar tinea pedis is commonly observed in these circumstances. The clinical appearance of onychomycosis varies depending on how it invades the nail, and laboratory test is always required to confirm diagnosis. Many factors affect the possible treatment

options, including kind of fungus and the no. of affected nails. Children may get the fungus indirectly through nail deformities or directly from their parents through environmental exposure.[8,9]

ETIOLOGY

Onychomycosis is a fungal infection of nails that can be caused by molds, yeast, and dermatophytes. About 90% of toenails and 75% of fingernail are affected by dermatophytes, especially trichophyton mentagrophytes and trichophyton rubrum. Other dermatophytes may cause Onychomycosis Include Epidermophyton floccosum, microsporum species, and various trichophyton species.[10] while yeast-based Onychomycosis is relatively uncommon with candida albicans being the causative agent, accounting for about 70% of yeast-related cases, non-dermatophytes Molds like Aspergillus and Fusarium species can also cause Onychomycosis, accounting for about 10% of cases worldwide. Other candida species, such as candida tropicalis and candida parapsilosis can cause Onychomycosis, especially in peoples with weakened immune systems or chronic mucocutaneous candidiasis.[11]

EPIDEMIOLOGY

Recent epidemiological research indicates that 5.5% of people worldwide are afflicted with Onychomycosis. According to a 2013 comprehensive review, Onychomycosis prevalence in North America and Europe varied between 4.3% in population based on research to 8.9% in hospital-based research. Condition appears to be on the rise, potentially due to factors such as increase life expectancy, modern footwear, obesity, and urbanization.[12] The frequency of the Onychomycosis rises with age, it affects adults more often than children in North America, the illness affects just 0.4% of youngsters, while up to 35% of the elderly might be affected. Males are more likely to have toenail Onychomycosis, while females are more likely to candida fingernail Onychomycosis. The risk of Onychomycosis can be raised by a no. of conditions, including as immunodeficiency, diabetes, obesity, chronic paronychia, and fungal infections elsewhere on the body.[13]

PATHOGENESIS

Onychomycosis arises when fungi such as molds, yeast, dermatophytes, or non-dermatophytes come into direct contact with nails. Nail unit is susceptible to fungal infection due to the ineffectiveness of its cell-mediated protection. Fungi can penetrate the nail plate by generating enzymes that breakdown lipids, protein, and keratin. If defenses against fungal infection are weakened, the chance of infection may increase.[14] The type and location of

fungal invasion determine clinical subgroups of onychomycosis develops. Furthermore, the formation of fungal biofilms in promotes in the development of antifungal resistance and helps the fungal evade antifungal therapies.[15]

CLINICAL FEATURES

Here are several common clinical signs of onychomycosis. The nail plate may turn yellow, green, brown, black, or white, which is a characteristic sign of nail discoloration. Moreover, the nail plate may expand, making trimming challenging, and become brittle or delicate, breaking and splitting readily.[16] It is also possible for nail plate to separate from nail bed, a process known as onycholysis. Furthermore, a typical trait is subungual hyperkeratosis, which is defined by the buildup of keratin debris beneath nail plate. Most prevalent kind of onycholysis is distal and lateral and subungual onychomycosis (DLSO), however there are other varieties as well. Both lateral and distal portions of the nail are impacted by DLSO.[14,17]

Other Types of Onychomycosis is are as follows

A) White Superficial Onychomycosis (WSO)

White, opaque spots that are readily scraped off are the consequence of fungal infection of nail plate. This disorder is identified by superficial colonization of nail plate and is usually caused by Trichophyton interdigitale.[18] However, invasive white superficial onychomycosis is caused by Fusarium spp. and other molds. Whitish or yellowish patches on the nail surface, patches may be circular, oval or irregular in shape. Nail surface may become rough or flaky. No significant thickening or deformation on nail plate.[19]

Fig. 1: WSO.

B) Proximal Subungual Onychomycosis (PSO)

Fungal components often produce a proximal leukonychia in the ventral nail plate. It is very rare for dermatophytes to cause proximal subungual onychomycosis (PSO), and historically. It was believed that PSO caused by T.ruburm was sign of HIV infection.[20] It manifests as a white area under proximal nail plate in lunula region. PSO is frequently associated with acute periungual inflammation and is common sign of a non-dermatophyte mold infection, particularly one caused by Aspergillus and Fusarium species. Examples of differential diagnosis include nail pustular psoriasis and acute bacterial paronychia.[21]

Fig. 2: Proximal Subungual Onychomycosis.

C) Dermatophytoma

Onychomycosis-specific dermatophytomas appears on the nail plate as linear, yellow, orange, and brown bands. Dermatophytoma is characterized by several distinct features. It typically involves the accumulation of fungal hyphae, which forms a compact mask beneath the nail plate.[22] This can lead to the nail plate separation, also known as onycholysis, subungual hyperkeratosis, where keratin debris builds up under the nail. If left untreated, Dermatophytoma can results in potential nail destruction. Additionally, the nail infection can cause pain and discomfort, as well as a foul odour emanating from the affected nail.[23]

Fig. 3: Dermatophytoma.

D) Tinea Pedis

A fungal illness called tinea pedis, commonly referred to as athlete's foot, affects skin of feet, especially in space between the toes.[24]

Fig.4 Tinea Pedis

E) DLSO

Distal (farthest) and lateral (side) portions of nail are impacted by DLSO (Distal Lateral & Subungual Onychomycosis), a kind of onychomycosis. Most prevalent clinical subtype of onychomycosis is distal lateral subungual. Fungal invasion in distal lateral subungual onychomycosis starts at the hyponychium and spreads to distal nail bed and then to nail plate. After that, fungus moves proximally through nail plate, creating spikes or linear channels.[16] Trichophyton rubrum is the most prevalent source of these clinical subgroup, while trichophyton mentagrophytes is less frequent. Distal lateral subungual onychomycosis manifests clinically as a yellowish, white, or brownish discoloration of nails distal corner. Onycholysis, onychauxis, and distal subungual hyperkeratosis of lateral and the distal portions of nail plate are frequently seen.[25]

Fig. 5: DLSO.

F) Endonyx Onychomycosis

An uncommon kind of fungal infection that only affects nail plate and doesn't damages nail bed is called as Endonyx onychomycoses. It is distinguished by unique clinical characteristics, such as milky white nail discoloration and lamellar cracking.[26] Notably, there is no sign of onycholysis or nail bed hyperkeratosis, and nail plate is still securely affixed to nail bed. Trichophyton soudanense or trichophyton violaceum are the two fungal species that usually cause this uncommon illness.[27]

Fig. 6: Endonyx Onychomycosis.

G) TDO

The most severe form of onychomycosis, known as Total Dystrophic Onychomycosis (TDO), it can be brought on by a protracted PSO or DLSO. Nail plate is yellowish, friable, and somewhat thickened. The severe subungual hyperkeratosis and complete dystrophic onychomycosis caused by aspergillus species are known as melanonychia.[28]

Fig. 7: Total Dystrophic Onychomycosis (TDO).

DIAGNOSIS AND DIAGNOSTIC STUDIES

To confirm and suspected case of onychomycosis, a mycological examination is necessary

which consist of 2 parts "Direct microscopic examination and culture". The direct microscopic examination involves treating nail material with KOH 40% and examine it under a microscope for hyphae and spores. However, KOH alone cannot identify the specific fungus causing infection, requiring culture for more accurate diagnosis. Histopathology of nail clipping can also aid in diagnosing onychomycosis, used in Periodic Acid-Schiff (PAS) stain to visualize fungal hyphae.[29] Digital Dermoscopy or Onychoscopy, is a quick and easy procedure which helps differentiate onychomycosis from common nail dystrophies. In cases of DLSO, Onychoscopy reveals distinct features, including a jagged edge with a sharp structure at the proximal margin, longitudinal striae of different colors, mottled discoloration resembling aurora borealis. Emerging diagnostic techniques include Confocal Laser-Scanning Microscopy (CLSM) which visualize dermatophyte's lengthy structure with high reflection.[30] Other innovative tools include dermatophyte test strips, fluorescence microscopy and Raman spectroscopy. Dermatophyte test strips is rapid, easy-to-use kit that detects trichophyton species using monoclonal antibody. It offers highly sensitive and negative predictive value, making it suitable for ruling out onychomycosis in uncertain cases.[31]

The potassium hydroxide (KOH), preparation is a valuable diagnostic tool for detecting fungal infection. It is a low-cost, rapid test that can help rule out fungal presence. To perform the test, drop of 10-20% KOH is added on nail specimen on glass slide, and then examined under a light microscope. If necessary, gentle heating can accelerate the process. Positive test result shows fungal hyphae, spores, yeast cell.[32] However, it doesn't provide information on specific fungal species or its viability. PCR testing allows for rapid a highly specific amplification of fungal DNA fragments. Accurate identification of the causative dermatophyte is possible with the PCR approach. The outcomes are also accessible in a matter of days rather than weeks. However, PCR assays are costly and easily available which decrease their use in general practice.[33]

COMPLICATIONS

Onychomycosis can lead to several complications, including pain and discomfort, especially if the infection is severe or has spread to other parts of the nail or surrounding tissue. The infection can also cause permanent damage to the nail, leading to thickening, brittleness, or crumbling of the nail. Furthermore, onychomycosis can increase the risk of secondary bacterial infection, which can lead to more severe complications.[34] In some cases,

onychomycosis can also increase the risk of cellulitis, a bacterial infection causes the skin and underline tissues. Rarely, onychomycosis leads to osteomyelitis, a bacterial infection of the bone. Additionally, onychomycosis can significantly impair quality of life, causing emotional distress, social embracement and functional impairment.[35]

TREATMENT

The severity of the illness and the clinical presentation determine the treatment strategies for onychomycosis. Oral treatment has limitations due to potential drug interaction and liver toxicity. The tropical antifungal therapies are often in effective without nail debridement. A combine approach using oral and tropical treatment is often most effective. There are following types of treatment are used.

1) Tropical Treatment

Tropical antifungal treatments for onychomycosis required specialized formulation to penetrate nail plate. However, this treatment is often limited by poor nail penetration, leading to high relapse rates of 20-25% of the patients.[36] Combining tropical treatments with systemic antifungals, debridement or nail avulsion can improve outcomes in severe cases. Nail lacquers, such as amorolfine 5% and ciclopirox 8%, can be effective for mild cases of onychomycosis, with treatment duration ranging from 6-12 months. Newer tropical treatments, including efinaconazole 10% solution and tavaborole 5% solution, have shown promise in treating dermatophyte-induce onychomycosis.[37]

Tavaborole, a tropical nail lacquer, has been approved for treatment of toe nail onychomycosis in US. Clinical research shown that it is safe and effective. Other potential treatment includes terbinafine nail solution and sprays, as well as luliconazole, which has shown positive result in clinical trials. Photodynamic therapy (PDT) and laser system are also emerging as therapeutic options.[38] PDT systems such as Nd ”YAG” laser and diode laser have shown promising results in clinical trials. However, further studies are needed to establish efficacy and optimal treatment protocols for this alternative therapies.[39]

2) Systemic Treatment

Severe cases of onychomycosis. Such as Distal Lateral Subungual Onychomycosis (DLSO) extending to proximal nail, Proximal Subungual Onychomycosis (PSO) caused by dermatophytes, and deeply in filtrating in white superficial onychomycosis required systemic treatment. Fluconazole, itraconazole and terbinafine are effective treatment achieving

mycological cure in 90% of finger nail infection and 80% of toe nail infection. However, treatment failure can occur due to clinical characteristics, etiological agents, and patient comorbidities.[40] systemic onychomycosis can be treated with terbinafine, itraconazole and fluconazole. Terbinafine can be administered as continuous therapy at 250 mg/day for 12 weeks or as a pulse therapy at 500 mg/day for 4 weeks on and 4 weeks off. Itraconazole is administered in pulse therapy at 400 mg/day for 1 week/month for 2-3 months.[41] Fluconazole is also an option, although it is less effective, with weekly doses of 150-300 mg for over 6 months. Combining systemic antifungal with tropical nail lacquer can enhance treatment outcomes a periodic removal of affected nail plate can accelerate improvement. New treatment options, such as posaconazole and albaconazole, are emerging as alternative therapy options.[42] However, treatment consideration must be taken to account, including the potential for non-dermatophyte moles to not to respond to systemic antifungal and a need for careful evaluation for candida onychomycosis due to association with diabetes of immune depression. In certain situation, nail paste may need to be avulsed surgically or chemically.[43]

3) Photodynamic Treatments

Photodynamic Therapy (PDT) is treatment approaches utilizes light to active photosensitizer, resulting in formation of reactive oxygen species which destroy fungal cells. The photosensitizer is absorbed by the fungus, making it more susceptible to the distraction than surrounding healthy tissues. Various photosensitizer has been used, including 5-Aminolevulinic Acid (5-ALA) and Methyl Amino Levulinate (MAL).[44] While data on PDT onychomycosis are limited, a 2016 systematic revies suggested it potential benefit. Adverse events such as mild pain and erythema, where well tolerated. Additionally, recent research has shown that PDT is a successful treatment for onychomycosis. However, large scale, randomized study are necessary to confirm efficacy of PDT and established formal recommendation for its use.[45]

4) Miscellaneous

Nail preparations and enhancement of tropical treatment

To enhance the effectiveness of tropical antifungal treatments, nail preparation techniques such as abrasion, trimming avulsion, and debridement can also be applied for increasing penetration and reduce fungal load.[46] For white superficial onychomycosis, mechanical removal of affected area followed by tropical antifungal therapy can be effective. Surgical avulsion is more invasive option but the novel devices like the nail drill system and derma

roller can facilitate control micro-penetration of nail without causing damage.[47] Additionally, keratolytic agents like urea and salicylic acid can enhance delivery of the tropical antifungal agent into nail. Studies have shown that tropical urea can improve the efficacy of antifungal treatments and soften the thick dystrophic nail. Combination therapies, such as K101 nail solution with oral terbinafine or itraconazole have also demonstrate improve clearance of onychomycosis.[48] Furthermore, phosphoric acid gel and iontophoresis have been exploded as method to enhance delivery of tropical antifungal agents into nail plate.[49]

CURRENT & FUTURE DEVELOPMENTS

❖ Novel Antifungal Agents and Treatment Method

Several novel broad-spectrum oral antifungal agents have shown promising results in treating onychomycosis, including posaconazole (Posanol, Noxafil), albaconazole (Code Name: UR-9825), Ravuconazole (Code Name: BMS-207147, ER-303456), Fosravuconazole, VT-1161, P-3061. Tropical antifungal agents that have shown promise include tazarotene (Tarzorac), Lanoconazole (Astat), luliconazole (Luzu, Luzan, Lulicon), NCV-422, & ME-1111.[50]

❖ Recent Development in Onychomycosis Treatments

Disclose as synthetic antifungal peptide, NP213 (Novexatin), which has shown promise in treating onychomycosis. Non thermal plasma has been investigated for treatment of onychomycosis. Additionally, researchers have explored the used of propolis, a natural product derive from the honey bees, in treating onychomycosis. Others treatments being investigated include the use of hydroxypropyl chitosan, redox gas solutions and ultrasound-enhance drug delivery.[51]

❖ Biofilms and Onychomycosis

Fungal biofilms have been identified as a potential factor in the persistent and recurrence onychomycosis.[52] Diagnostic test to detects biofilms are needed, and device-based therapies which can destroy biofilms and are explored. The use of nanoparticles in the tropical antifungal agents has also shown promise in enhancing drug penetration and efficacy.[53]

❖ Standardization of treatment outcome measures

Lack of standardized definitions for treatment outcome measure in onychomycosis make it challenging to compare data across study. It is essential to establish unified definitions for clinical cure, almost complete cure, clinical success, and clinical improvement to facilitate to

consistent reporting and comparison of treatment outcomes.[54]

CONCLUSION

Onychomycosis, a prevalent fungal infection, necessitates personalized treatment. Due to the slow nail growth especially in older adults, treatment duration can span several months. Choice of treatment depends on type, severity, underline health condition of patient. Mild cases, typically involving toe nails, can be treated with tropical antifungal and occasional nail remover. However, more severe cases such as those are affecting the proximal nail or cause dermatophytes, required systemic treatment with fluconazole, itraconazole, or terbinafine. Additional research is needed to standardized protocol for laser and photodynamic therapies.

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