Original Article

Brief Overview About Onychomycosis

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Abstract

Background: Onychomycosis is derived from the Greek words' "onyx" meaning nail and "mykes" meaning fungus. It has been known that onychomycosis in children is less common than in adults, but its frequency has been rising. Very well-established predisposing factors for onychomycosis are trauma, old age, and previous infections with tinea pedis, poor nail trimming, sports and fitness activities, smoking, occlusive shoes, asymmetric gait nail unit syndrome and hallux valgus, comorbidities, such as diabetes, obesity, immunosuppression and malignancies are also associated with increased risk, also it is more common in psoriatic patients than healthy individuals and it is estimated that psoriatic patients have a 50% chance of developing onychomycosis compared with non-psoriatic patients. Biofilms have recently been acknowledged to play an important role in the pathophysiology of onychomycosis. Although fungi were previously thought to be planktonic (defined as in suspension, free floating, and acting independently), recent evidence supports the formation of biofilms. Suggested mechanism of biofilms is that they are stationary and not moving microbial communities that are fixed to biological surfaces (such as the nail plate) via an extracellular matrix that enclose the biofilms, so they contribute to resistance to antifungal agents, increased virulence and invasion of immune systems. Dermatophytes, NDM and yeast all form biofilms in vitro especially T. rubrum and T. mentagrophytes begin forming biofilms after 3 hours and are fully formed by 72 hours. Dermatophytes cause about 90% of toenail and 75% of fingernail onychomycosis mainly anthropophilic dermatophytes particularly by T. rubrum and T. mentagrophytes. Non-dermatophyte molds (NDM) that can cause onychomycosis account for 20% of cases worldwide and include Aspergillus species, Scopulariopsis species, Fusarium species and Acremonium species; Yeast onychomycosis is caused mainly by Candida Albicans as about 70% of all yeast infection, the rest is caused by Candida tropicalis and Candida parapsilosis, patients with chronic mucocutaneous candidiasis and immunodeficiency are more likely infected with the yeast organisms, especially in the fingernails

Keywords: Onychomycosis

INTRODUCTION

Onychomycosis is derived from the Greek words' "onyx" meaning nail and "mykes" meaning fungus**.** It has been reported that patients are genetically susceptible to dermatophyte infections in an autosomal dominant pattern**.** Very well-established predisposing factors for onychomycosis are trauma, old age, and previous infections with tinea pedis, poor nail trimming, sports and fitness activities, smoking, occlusive shoes, asymmetric gait nail unit syndrome and hallux valgus, comorbidities, such as diabetes, obesity, immunosuppression and malignancies are also associated with increased risk, also it is more common in psoriatic patients than healthy individuals and it is estimated that psoriatic patients have a 50% chance of developing onychomycosis compared with non-psoriatic patients **(1).**

Dermatophyte toenail infection are prevalent among members of a common residence and the risk of transmission to other members when a member is affected is approximately 44% to 47%. Biofilms have recently been acknowledged to play an important role in the pathophysiology of onychomycosis. Although fungi were previously thought to be planktonic (defined as in suspension, free floating, and acting independently), recent evidence supports the formation of biofilms. Suggested mechanism of biofilms is that they are stationary and not moving microbial communities that are fixed to biological surfaces (such as the nail plate) via an extracellular matrix that enclose the biofilms, so they contribute to resistance to antifungal agents, increased virulence and invasion of immune systems. Dermatophytes, NDM and yeast all form biofilms in vitro especially T. rubrum and T. mentagrophytes begin forming biofilms after 3 hours and are fully formed by 72 hours **(1).**

Pathogenic organisms:

Dermatophytes cause about 90% of toenail and 75% of fingernail onychomycosis mainly anthropophilic dermatophytes particularly by T. rubrum and T. mentagrophytes. Non-dermatophyte molds (NDM) that can cause onychomycosis account for 20% of cases worldwide and include Aspergillus species, Scopulariopsis species, Fusarium species and Acremonium species; Yeast onychomycosis is caused mainly by Candida Albicans as about 70% of all yeast infection, the rest is caused by Candida

tropicalis and Candida parapsilosis, patients with chronic mucocutaneous candidiasis and immunodeficiency are more likely infected with the yeast organisms, especially in the fingernails **(2).**

Clinical types of onychomycosis:

Based on the pattern of invasion, onychomycosis can be divided into the five clinical subtypes. It should be noted that patients may have a combination of these subtypes: distal and lateral subungual onychomycosis (DLSO) , white superficial onychomycosis (WSO), proximal subungual onychomychosis (PSO), endonyx onychomychosis, total dystrophic onychomycosis (TDO) **(2).**

Distal and Lateral Subungual Onychomycosis:

Distal lateral subungual onychomycosis is the most common clinical subtype, in DLSO, the fungal invasion begins at the hyponychium and then continues to involve the distal nail bed and eventually the nail plate resulting in formation of linear channels "spikes". Clinically,DLSO presents as yellowish, whitish, or brownish discoloration of a distal corner of a nail, distal subungual hyperkeratosis, onycholysis, and/or onychauxis of the lateral and distal aspects of the nail plate are common**,** DLSO usually affects one or both of the great toenails and is usually associated with tinea pedis . **White Superficial Onychomycosis**

In WSO the upper surface of the nail plate is affected by the fungus,especially T. mentagrophytes , WSO manifests as white dots or patches on the surface of the nail plate The white dots and patches can be easily scraped off **(3).**

Figure (1): White superficial onychomycosis (WSO): white opaque friable patches of the nail plate. (4)

Proximal Subungual Onychomycosis:

Proximal subungual onychomycosis manifests when the fungus attack the under surface of the PNF at the periphery of the cuticle then extends distally, PSO appears clinically as an area of leukonychia in the proximal nail plate and moves distally with nail growth producing subungual hyperkeratosis, proximal onycholysis, leukonychia, and destruction of the proximal nail plate. Proximal subungual onychomycosis due to dermatophytes is very rare. PSO due to T. rubrum was considered as a sign of HIV infection. PSO is a common presentation of NDM infection (Fusarium spp.) and acute paronychia is often associated **(4).**

Figure (2): Proximal Subungual Onychomychosis: white discoloration of the proximal nail plate (4).

Endonyx Onychomycosis

It's caused by infection of the nail plate sparing the nail bed, the main organism is T.soundanense and T. violaceum, clinically characterized by milky patches of the nail plate, indentations, and lamellar splitting, the nail plate is adherent to the nail bed and subungual hyperkeratosis is missing **(1).**

Figure (3): Endonyx onychomycosis: white discoloration of the nail plate that is firmly attached to the nail bed (4).

Total Dystrophic Onychomycosis(TDO):

Total dystrophic onychomycosis often implies the final stage of onychomycosis as it follows any ather subtype it appears as total destruction of the whole nail apparatus**.** Clinically, TDO presents with a severely dystrophic and crumbed nail plate showing yellow discoloration, thickening and being friable.In addition to being the most difficult stage, it also comes with the highest risk of developing subungual ulcerations, secondary bacterial infection and precipitating gangrene in patients with impaired peripheral circulation **(5).**

Figure (4): Total onychomycosis: the nail plate is completely invaded by fungi and friable (4).

Candidal Onychomycosis (CO.):

Candidal onychomycosis is defined as a distiguished entity in the new classification of onychomycosis and also is subdivided into more categories as (i) chronic paronychia with secondary nail dystrophy; (ii) distal nail disease; (iii) mucocutaneous candidiasis and (iv) secondary candidiasis **(6).**

Figure (5): Candida onychomycosis of long duration with paronychia (7).

Fungal melanonychia:
Fungal melanonychia is characterized by brown to black pigmentation of the nail unit; it can be accompanied by a dystrophic and raised plate, secondary to subungual hyperkeratosis. It is common to observe periungual inflammation, it can be longitudinal *(*T. rubrum var. nigricans*)* or diffuse brown pigmentation *(*Neoscytalidium dimidiatum and Aspergillus niger*)*, In longitudinal melanonychia, the band of pigmentation is wider distally and tapers proximally (distal to proximal extension of infection), a variant of the superficial white onychomycosis can be referred to as superficial black onychomycosis. It is commonly caused by Aspergillus niger and frequently accompanied by periungual inflammation and black pigmentation of the proximal nail fold **(8)**.

Figure (6): (a) Candida paronychia and onycholysis in a diabetic patient. (b) Paronychia by Candida in a patient with HIV-AIDS. (C) Fungal melanonychia with a greenish or brownish discoloration. (d) Granulomatous onyxis in a patient with chronic mucocutaneous candidiasis. (e) Direct examination (KOH), multiple yeasts are observed (40×) **(9).**

<u>Diagnosis of onychomychosis:</u>
Precise diagnosis is critical as onychomycosis is transmissible between humans and has effects on patients' quality of life, a combination of clinical examination with mycological testing ensures accurate diagnosis. Standard diagnostic tools include KOH, direct microscopy, fungal culture are considered the golden standards of diagnosis alongside with new tools as dermoscopy, reflectance confocal microscopy and artificial intelligence, or mycologically, such as molecular assays **(10).**

Direct microscopic examination:
Potassium hydroxide (KOH) testing uses a KOH solution (typically 10–20% KOH) to reduce keratin in nail samples, improving visualization of fungal structures under light microscopy. A variety of stains may be added with KOH to increase

visualization. Calcofluor white (CW) highlights hyphal walls from surrounding debris under a fluorescent microscope **(11).**

Fungal Culture:

Fungal culture is considered the gold standard; however, it has several disadvantages such as a high rate of false negative results, it may take up to 4 weeks **(12).**

False-negative results can be generated in 40 % of the cases that are microscopically positive **(13).**Culture is performed on Sabouraud dextrose agar (SDA) with antibiotics such as gentamicin or chloramphenicol to inhibit bacterial growth and cycloheximide (Actidione®) to inhibit growth of molds, but if NDM or a yeast are suspected, SDA without Actidione® is used **(11).**

However dermatophyte Test Medium (DTM) can be used, it contains antibacterial to inhibit bacteria and red phenol as indicator that change medium color from yellow to red if a dermatophyte grows, it is convenient to put in the tube or in the Petri dish small fragments of the nail or to pulverize the sample **(14).**

Cultures must be incubated at room temperature (24–28° C), and the colonies can be observed from 1 week to 1 month, but NDM and yeasts can grow in less than 1 week. Culture is considered negative after 3–6 weeks. If negative, it could be convenient to repeat the complete mycological study **(15).**

If a dermatophyte is isolated by culture, there is immediate pathogenic confirmation, unlike the necessary repeated inoculates required to confirm non-dermatophyte mold pathogenesis**.** Adequate quantity of samples increases chances of having positive results in comparison to smaller amounts as the sampled section of nail may have scanty pathogens **(16).**

Dermoscopy:

Dermoscopy is an available , noninvasive, rapid and simple diagnostic method that allows visualization of morphologic features which are not visible by the gross picture . Diagnosis of onychomycosis by dermoscopy can help to avoid microbiological techniques.

The diagnostic dermoscopic signs of onychomycosis are:

(1) proximal margin of the onycholytic area showing jagged edge, with sharp structures, directed to the proximal fold.

(2) longitudinal striae of different colors in the onycholytic nail plate.

(3) the overall appearance of the color of the affected nail plate in a matted variable discoloration resembling the aurora borealis **(17).**

- **New approaches in diagnosis:**

(1) Molecular Biology:

Molecular polymerase chain reaction (PCR) is a technique used in microbiology that amplifies a segment of DNA across several orders of magnitude, it can increase the number of a small portion of sequestrated fungal DNA sequence within a range of 24 to 48 hours' range. PCR allows a less subjective approach and a lower false-negative outcome compared with other methods. The only Flaws of this method are the cost and the potential positive identification of a noninvasive organism (false positive) **(11).**

(2) Mass spectrometry:

Mass spectrometry, matrix-assisted laser desorption or ionization time-of-flight mass spectrometry (MALDI-TOF) is a more recent technique that ionizes chemical species and sorts the ions based on their mass-to-charge ratio, this technique has been used pre- viously in bacterial identification and has recently been applied to yeast and moulds it can also effectively identify clinical dermatophyte isolates and drastically reduce response times **(18).**

(3) Dermatophyte test strip:

Detects dermatophytes through immunochromatography using monoclonal antibodies that react with polysaccharides present in the cell wall, This antibody was found to react specifically with seven dermatophytes; T. rubrum, T. mentagrophytes, T. violaceum, T. tonsurans, M. gypseum, M. canis and E. floccosum , This test can be quick, precise , rapid in a clinical setting, has a good detection capacity and be a reliable method to test for onychomycosis **(19).**

(4) Confocal laser-scanning microscopy (CLSM), Reflectance confocal microscopy (RCM):

A new diagnostic technique, Reflectance confocal microscopy enables clinicians to observe bright filamentous septate hyphae at near histologic resolution by the bedside, It uses a 830 nm laser in reflectance mode which divides the nail unit into thin horizontal sections for examination, Reflectance confocal microscopy of onychomycosis reveals networks of bright filamentous septate hypha, it is expensive and not subsidized in many countries, and further studies are needed to support its utility in the clinical setting **(20).**

(5) Atrificial intelligence (AI):

Artificial intelligence may prompt patients to seek further assessment for nails that are suspicious for onychomycosis as Onychomycosis is an ideal candidate for AI as it is a common condition with minimal racial differences (**20).**

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