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Photodynamic therapy in treatment of onychomycoses

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Abstract
Onychomycosis (OM) is a global fungal illness that affects the nails. It is estimated to have a prevalence of around 5.5% to 8%, accounting for half of all nail infections. The etiological agents of OM, including dermatophyte molds (DM), yeasts (YST), and non-dermatophyte molds (NDM), use the keratinaceous material found in the nail plate as a source of energy. Several variables that increase the likelihood of developing OM have been identified, including immunosuppression, diabetes, obesity, smoking, nail trauma, onycholysis (separation of the nail plate from the nail bed), age, gender, and geographical location. PDT is a very appealing treatment method for OM, particularly since it has previously received approval from the Food and Drug Administration (FDA). PDT is a safe and minimally invasive treatment that involves the use of a photosensitizer (PS) in the presence of oxygen (O2).

Keywords: Onychomycoses, photodynamic therapy, treatment

Introduction
Onychomycosis is a prevalent and long-lasting infection of the nail caused by fungi such as dermatophytes, yeasts, or non-dermatophyte molds (NDMs). It is characterized by nail discoloration, separation of the nail from the nail bed (onycholysis), and thickening of the nail plate [1]. The clinical categorization is based on the precise location of the infection and encompasses distal and lateral subungual OM, proximal subungual OM, complete dystrophic OM, and superficial white OM. The most prevalent types among them are distal and lateral subungual OM [2].
Treating OM is difficult due to the fact that the infection has penetrated deeply into the nail [3]. Antifungal medications have been the primary treatment option for a significant period of time. In recent times, laser technologies have emerged as a remedy for OM, overcoming the drawbacks associated with systemic and topical medication treatments [2].
Prior studies have shown that Photodynamic treatment (PDT) effectively suppresses the growth of many fungi, including Trichophyton rubrum, Trichophyton mentagrophytes, Candida albicans, and other species. The experience of PDT in treating OM is limited [4].

Etiology of OM
1. **Predisposing factors:** Factors contributing to the increase in mycoses include the aging population, heightened use of immunosuppressive drugs, higher prevalence of underlying diseases like HIV and diabetes that weaken patients' immune systems, greater exposure to spas and public swimming pools, the use of tightly fitting shoes for fashion purposes, and long-distance running in athletic competitions [5].
2. **Causative organisms:** The etiological agents responsible for OM belong to the fungal kingdom and include dermatophytes, Candida (yeasts), and NDM. Dermatophytes are responsible for 90% of toenail OM and 50% of fingernail OM [6].
3. **Dermatophytes:** Dermatophytes have the potential to infiltrate keratinized tissue such as skin, hair, and nails. However, they are often limited to the nonliving outer layer of the skin (epidermis) due to their inability to enter healthy tissue in a person with a strong immune system [7].

Clinical varieties of OM

Distal subungual OM (DSO): This is the most prevalent kind of OM, which is identified by the infiltration of the nail bed and the lower surface of the nail plate, starting at the hyponychium. The invading microorganism moves towards the origin of the nail via the underlying structure responsible for nail growth [8]. Figure 1.

Fig 1: The presence of Candida has induced distal subungual OM, characterized by onycholysis and subungual hyperkeratosis, resulting in yellow staining of many fingernails [9]

Endonyx OM (EO)

The nail bed is unaffected by the widespread penetration of the nail plate that characterizes endonyx OM. Impacted nails may appear milky white and have lamellar splitting when examined under a microscope. There has been no separation of the nail plate from the bed or excessive thickening of the nail bed, and the nail plate is firmly attached to the bed. The rare infection may be caused by either Toxoplasma soudanense or Toxoplasma violaceum [9]. Figure 2.

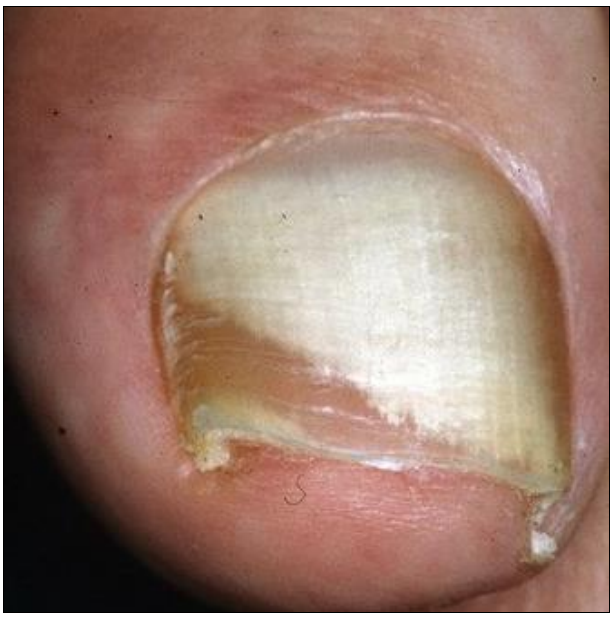

Fig 2: Endonyx OM: white discoloration of the nail plate that is firmly attached to the nail bed [9]

Proximal subungual OM (PSO)

PSO refers to a fungal infection that occurs on the inner layer of the nail plate. This infection originates from the eponychium and nail matrix. Consequently, the outcome of the KOH examination for an infected nail of PSO is often negative. Fungi infiltrate the upper surface of the nail and establish clusters that manifest as white, opaque structures that may be readily removed by scraping [9]. Figure 3.

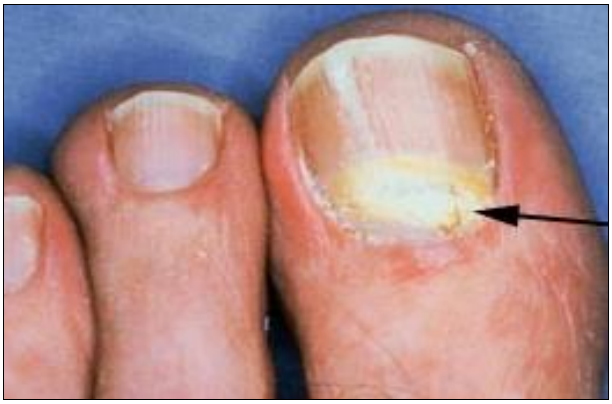

Fig 3: PSO (arrow) [10]

White superficial OM (WSO)

OM is a term used to describe a fungal infection that affects the outermost layer of the nail plate(s). Consequently, WSO exhibits visible white and scaly lines or patches on the nail plate, which may be readily removed via KOH testing [11]. Figure 4.

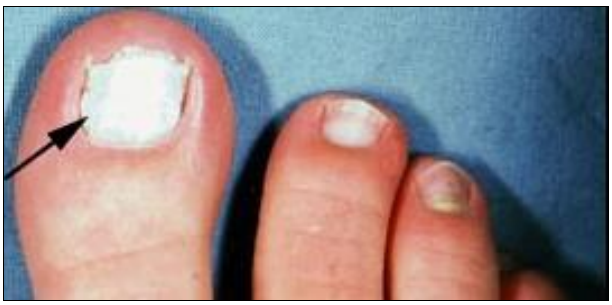

Fig 4: White superficial OM [10]

Total dystrophic OM (TDO)

It is the most advanced phase of OM, which may develop as a consequence of a persistent DLSO or PSO. The nail plate has a uniform thickening, fragility, and yellowish coration [12]. Figure 5.

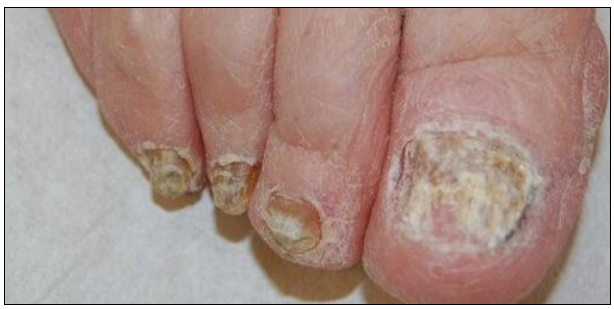

Fig 5: Total OM: the nail plate is completely invaded by fungi and friable [13]

Mixed pattern OM (MPO)

Illustrate several patterns of nail plate infection inside a single nail. The predominant patterns are PSO combined with SWO or DLSO combined with SWO [14].

Diagnosis of OM

The diagnosis of OM is transitioning from the use of clinic-pathologic instruments, which are time-consuming and provide false negative findings in about one third of cases, to a clinic-imaging approach using dermoscopy [15].

Clinical & dermoscopic examination

The predominant symptoms of OM are nail discolouration, nail hypertrophy, and sometimes onycholysis. Dermoscopy may be used for the assessment of the nail apparatus, also known as onychoscopy [16].

Direct microscopic examination

Direct microscopy of a 20% potassium hydroxide (KOH) mount and fungal culture are the standard laboratory procedures used for diagnosis. The use of a KOH mount offers a fast, simple, and cost-effective method for screening [17].

1. **Culture:** It remains the gold standard by which superficial fungal infections are diagnosed, with the added advantage that culture provides precise identification and can detect a wide range of fungal pathogens. However, fungal culture may take 5–7 weeks to provide results [18].
2. **Polymerase chain reaction (PCR):** This approach is very sensitive for diagnosing fungal infections. Directly applying PCR technology to clinical material enables prompt and precise diagnosis of OM. This will enable immediate and focused commencement of antifungal treatment [19].
3. **Histopathology:** Examining the distal nail plate using histopathological analysis, obtained from the nail clipping procedure, may be an extra diagnostic method for situations where OM is suspected based on clinical symptoms but consistently shows negative results in mycological tests [20].

Treatment of OM

Topical therapy: Topical antifungal treatments that are currently in use include ciclopirox 8% and amorolfine 5% lacquers. Both exhibit a wide range of effectiveness against yeasts, dermatophytes, and NDM. The concentration of amorolfine in the film is 25% after applying a 5% lacquer [21].

Systemic treatment

Oral terbinafine and oral itraconazole are the accepted treatments for this condition. However, both medications have a lengthy treatment duration, taking up to 6 months for fingernails and 12 months for toenails to be well cured [22].

- **Terbinafine:** It is the first line of treatment. In psoriatic patients it worsens symptoms. Dose of the drug is 250 mg/day for 6 weeks for fingernails or (3-12) months for toenails [23].
- **Itraconazole:** This is the second course of therapy. The suggested dose schedule involves two therapy pulses, with each pulse comprising of 200 mg taken twice day (400 mg/day) for a duration of one week. There is a 3-week interval during which itraconazole is not administered between each pulse [24].
- **Fluconazole:** It is considered the third line of treatment. Dose is (150 -450) mg once weekly for three months for fingernails and for 6 months for toenails. Abdominal discomfort, nausea, diarrhea, flatulence, rash, headache [25].
- **Griseofulvin:** It is considered the fourth line. For fingernails dose: (500, 1000) mg daily for (6-9) months, and the same dose for (12-16) months in toenails [26].

PDT: PDT is a form of treatment which involves a chemical substance called photosensitizer and a source of light. It aims to select and kill cancer cells. It can also be used to treat some skin and eye diseases [27].

Mechanism of action of PDT

The molecular mechanism of photodynamic treatment relies on the synergistic interactions between three non-toxic components, resulting in targeted effects only inside diseased tissues [28].

- The photosensitizer (PS) is a substance that reacts to light and produces a chemical or biological effect.
- Illumination with the suitable wavelength.
- Oxygen is present in the cells in a dissolved state.

The mechanism of action of PDT relies on two distinct physico-chemical processes: type I and type II reactions [28].

Type I reaction: The process takes place by producing very reactive free radicals (O2 −, H2O2, OH−), leading to a diverse combination of ROS, which have the ability to oxidize various biomolecules [29].

Type II reaction: The process relies on the production of singlet oxygen, a very reactive form of oxygen, via an excited-state interaction between a photosensitizer molecule in an excited state and a crucial oxygen molecule [30].

Technique used in PDT

PDT can be administered through surface illumination, as in skin or intra-operative PDT, where broad beam illumination is used. Alternatively, interstitial PDT can be employed for deeply seated tumors that are locally advanced (>1 cm). In this case, a light delivery probe is inserted directly into the target area, and light is emitted from within the tumor [31]. Photodynamic treatment consists of two distinct stages. Initially, a photosensitizer is provided to the patient, usually by injection, and it gathers in cells that are quickly multiplying. The duration of absorption into the patient's body varies depending on the particular photosensitizing chemical used, usually taking place within a timeframe of 6 to 48 hours [32].

Photosensitizers

Photoactive molecules are capable of absorbing light energy and initiating the production of ROS for the process of PDT [33]. The PS Photofrin was the first photosensitizer agent to get approval from the FDA. The categorization of photosensitizers may be based on their chemical composition, which includes porphyrin-based PS (such as photofrin and ALA), chlorophyll-based PS (such as chlorins and purpurins), and dyes (such as phthalocyanine and naphthalocyanine) [34].

Dye Photosensetizers

- **Methylene blue:** Methylene blue (MB) is a member of the phenothiazinium family and has an absorption wavelength of 666 nm [35]. This sensitizer specifically targets melanoma cells and has favorable PDT effects on melanoma cell cultures. Methylene blue is used in clinical PDT for the treatment of basal cell carcinoma and Kaposi's sarcoma. Additionally, it is employed in *in vitro* testing of adenocarcinoma, bladder carcinoma, and Henrietta Lacks (HeLa) cervical tumor cells [36].
- **Porphyrins:** Biocompatible porphyrins and their

derivatives possess an elongated conjugated electronic structure, which is mostly detectable by NIR absorption extinction molar constant, and exhibit satisfactory fluorescence quantum yields. The many characteristics of nanoconjugates generated from porphyrin make them very applicable in several biological sectors, such as PDT and triplet sensitization [37].

- **Chlorophylls (Chls):** Chlorophyll derivatives that occur naturally and have chlorin substitutions. Chlorophyll a and chlorophyll b are present in all green plants and are the most prevalent natural chlorophylls. They exhibit an absorption band with the longest wavelength that changes to the region of 650 to 690 nm and significantly rises in intensity, which are extremely advantageous for photosynthesis [31].

Light sources for PDT

PDT light sources include a variety of options, such as laser light, powerful pulsed light, light-emitting diodes (LEDs), blue light, red light, and several other visible lights, including natural sunshine [38]. Every light source transforms the energy it receives into light. In an incoherent light source, such as a lightbulb, light is produced by spontaneous emission, where photons are released in a random manner by the stimulated atoms. This phenomenon emits radiation uniformly in all directions, exhibiting a range of wavelengths and without any correlation between individual photons [39].

1. **Laser:** Traditionally, argon lasers and metal vapor lasers were the primary options for PDT. These devices were highly favored for PDT therapy [40]. The excimer laser is used to eradicate fungus by administering small amounts of radiation. Further measurements are necessary to determine the modulation parameters of the excimer laser radiation used in the treatment of OM [41].
2. **Intense pulsed light (IPL):** The decision to use IPL as a light source for PDT is justified by the absorption spectrum of the photosensitizer and the characteristics of IPL. Protoporphyrin IX (PpIX) has absorption maxima at wavelengths of 505, 540, 580, and 630 nm. The emission spectrum of IPL spans from 500 to 1200 nm [42]. In addition to wavelength, many treatment parameters such as pulse duration, pulse sequences, and pulse delay time may be adjusted on most devices, allowing users to have more flexibility and accuracy. Hence, a notable advantage of IPL devices lies in their capacity to address diverse objectives using a single device via the use of distinct filters [43].
3. **Light Emitting Diodes (LED):** Semiconductor devices are characterized by the generation of light resulting from the recombination of electrons and holes. The production of light in an LED operates on the same fundamental concept as a diode laser. However, unlike diode lasers, LEDs lack a resonant cavity for stimulated emission and instead generate light spontaneously [39]. These devices are often compact and easy to carry, allowing for the implementation of innovative treatment approaches such as extended or repeated (metronomic) PDT [44].
4. **Blue and red light:** Red or infrared light is used for the treatment of the epidermis. Upon exposure to light, the epidermis assimilates it and subsequently triggers the production of collagen proteins. Therefore, it is used in the process of revitalizing the skin. In contrast, blue light specifically targets the sebaceous glands. The hair follicles are situated underneath them. Consequently, it is used for the therapeutic management of acne [38].

Indications of PDT

Table (1) [45] shows the dermatological indications of PDT.

Table 1: Dermatological indications for PDT [45]

Oncological	Inflammatory	Infectious	Cosmetic
Actinic keratosis	Acne	Verrucae vulgares	Photo-chemo-rejuvenation
Superficial BCC	Psoriasis	Condylomata acuminate	-
Bowen disease	Darier disease	Cutaneous leishmaniasis	-
Cutaneous lymphomas	Lichen planus	-	-
Epidermotropic metastases	Rosacea	-	-
Kaposi sarcoma	-	-	-

Side effects of PDT

Similar to any medical intervention, PDT has the potential for adverse reactions. Photosensitizing drugs have an impact on both diseased and normal cells, causing patients to become more susceptible to light even after the therapy has concluded. The skin and eyes may exhibit heightened photosensitivity for a duration of up to three months after the operation [44].

Other possible side effects of PDT include [46]

Edema occurring at or in close proximity to the site of skin treatment. Skin pigmentation alteration. The skin during treatment may exhibit scales, crusts, or blisters. Sensations of pruritus, paresthesia, or inflammation. Dermatological infections.

Contraindications of PDT

The patient has an unresponsive tumor and a medical history that includes porphyria, systemic lupus erythematosus, photosensitive dermatoses, and an allergy to the active components in the Ps, which is a very uncommon condition [47].

Conclusion

Photodynamic therapy is a safe option for treatment of onychomycosis for all studied clinical types of onychomycosis with different types of isolated fungi. Photodynamic therapy was a valuable treatment option of onychomycosis as it was safe, minimal time consumption and helpful in fungal species resistant to medical treatment such as aspergillus species.

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