Chapter 7
Onychomycoses Due to Non-dermatophytic Molds

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Key Features

- Non-dermatophytic molds have been increasingly recognized as agents of onychomycosis.
- Prevalence of non-dermatophytic onychomycosis depends on geographic areas.
- Molds can cause different types of onychomycosis including proximal subungual, "deep" white superficial, and distal subungual onychomycosis.
- Diagnosis of mold onychomycosis is more complex than the dermatophytic counterpart and requires microscopic examination and culture on multiple samples.
- Treatment is difficult and often requires combination of topical antifungals, systemic antifungals, and chemical avulsion.

Introduction

Non-dermatophytic molds are filamentous fungi that are regularly found in nature as soil saprophytes and plant pathogens. Molds can frequently colonize the nails and be isolated in cultures without having a pathologic significance. However, molds can also invade the nails and cause onychomycosis, and prevalence of mold infections has been increasing worldwide in the last several decades. Diagnosis of mold onychomycosis requires a strict correlation between nail abnormalities and mycologic findings as well as isolation of the same organism from multiple samples and inoculates. Concomitant infections with molds and dermatophytes can also occur.

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A. Tosti et al. (eds.), *Onychomycosis*, DOI 10.1007/978-3-319-44853-4_7

Molds that can cause onychomycosis include but are not limited to *Scopulariopsis brevicaulis*, *Aspergillus* spp., *Acremonium* spp., *Alternaria* spp., *Chrysosporium* spp., *Aureobasidium pullulans*, *Curvularia* spp., *Penicillium* spp., *Fusarium* spp., *Onychocola canadensis*, *Exophiala* spp., *Ulocladium* spp., *Nattrassia mangiferae*, and *Neoscytalidium dimidiatum* [1, 3, 7, 14, 17–19, 33, 42].

Prevalence of mold onychomycosis varies in different countries depending on geographic area, climate, and lifestyle conditions [4]. Incidence of the infection increases with age, with most patients being older than 40 years [1, 4, 6, 8, 18, 42].

Treatment of mold onychomycosis is even more difficult than dermatophytic onychomycosis. Combination of topical antifungals, chemical nail avulsion, and systemic antifungals is often required.

Epidemiology

Approximately 10 % of onychomycoses are caused by non-dermatophytic molds [2, 5, 14]. Frequencies as high as 22 % [30], 45.8 % [17], 51.6 % [36], and even 68 % [44] have been reported in various countries. Data in the United States is limited since most doctors do not take a culture sample (Table 7.1).

Most cases of mold onychomycosis are caused by *Scopulariopsis brevicaulis* [3, 11, 20, 37, 38, 40, 43] or *Aspergillus* spp. [4, 18, 30, 41, 42, 44]. Most infections of non-dermatophytic molds are found in the hot and humid tropical and subtropical parts of the world [3, 21, 30]. Prevalence varies globally, depending on the climate and microenvironment of each geographic region. *Acremonium* spp., *Aspergillus* spp., and *Neoscytalidium* spp. are common in Canada [32]. *Fusarium* spp., *Acremonium* spp., and *Scopulariopsis brevicaulis* are common in the United States [45]. *Neoscytalidium* spp. and *Fusarium* spp. are found throughout South America (especially prevalent in Colombia and Brazil) [33, 35]. *Scopulariopsis brevicaulis*, *Aspergillus* spp., and *Fusarium* spp. are frequently isolated in Pakistan [36]. *Neoscytalidium dimidiatum* and *Fusarium* spp. are found in Thailand [36], while *Scopulariopsis brevicaulis*, *Aspergillus* spp., *Acremonium* spp., and *Fusarium* spp. are common in the Mediterranean (Italy, Greece, and Turkey) [37–39, 42].

The most important predisposing factor is, as for dermatophytes, patient's age. Studies of non-dermatophytic mold onychomycosis report most afflicted patients being older than 40 years [1, 4, 6, 8, 18, 43]. Possible reasons include slower nail growth rate with aging, repeated nail trauma, prolonged exposure to pathogenic fungi, and venous insufficiency. Toenails are generally more often affected than fingernails, due to their slower growth rate.

Onychomycosis from non-dermatophytic molds is more common in females, in contrast to dermatophytic onychomycosis [1, 31, 32]. In a Colombian study of 310 cases of non-dermatophytic mold onychomycosis with toenail infections, women represented 62 % of cases [31].

Table 7.1 Percentage of non-dermatophytic mold onychomycosis due to mold pathogens in different countries

	United States [45]	Canada [32]	Iran [41]	Brazil [33]	Colombia [34]	Pakistan [35]	Thailand [36]	Italy [37]	Greece [38]	India [4]	Turkey [42]
Total percentage of onychomycosis due to NDM	20.7 %	4.3 %	11.5 %	7.4 %	14 %	11 %	51.6 %	9 %	15.5 %	35.3 %	9 %
Scopulariopsis brevicaulis	20.5 %	–	2.1 %	–	–	18.2 %	–	35.3 %	65.9 %	3.8 %	3 %
Aspergillus species	11.4 %	33 %	59.6 %	8.1 %	–	18.2 %	–	27.5 %	4.5 %	85 %	22 %
Acremonium species	29.5 %	33 %	17 %	–	–	9.1 %	–	5.9 %	22.8 %	–	18 %
Neoscytalidium species	4.5 %	17 %	–	–	38 %	9.1 %	70.6 %	–	–	–	–
Fusarium species	34.1 %	–	12.7 %	60.8 %	42.9 %	36.4 %	29.4 %	27.5 %	–	3.8 %	18 %
Nattrassia mangiferae	–	–	–	31.1 %	–	–	–	–	–	–	–
Alternaria species	–	–	–	–	–	9.1 %	–	–	4.5 %	–	3 %
Ulocladium species	–	–	–	–	–	–	–	–	–	–	12 %

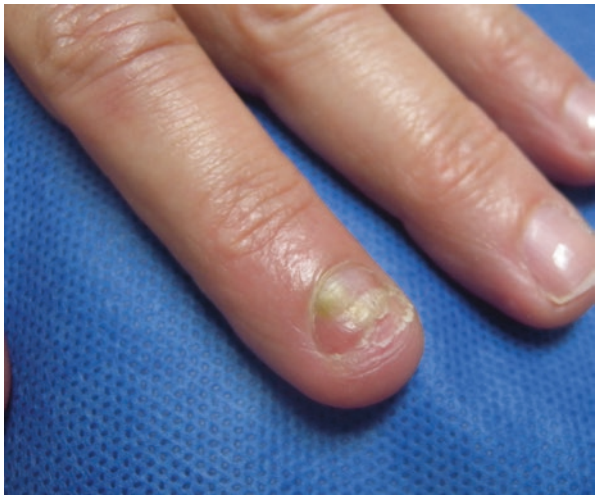

Fig. 7.1 Proximal subungual onychomycosis with periungual inflammation due to *Fusarium* spp.

Clinical Features

Non-dermatophytic molds can cause proximal subungual, "deep" white superficial, and distal subungual onychomycosis.

Proximal subungual onychomycosis is characterized by the invasion of the nail matrix through the proximal nail folds. Fungi are then incorporated in the ventral nail plate from the matrix. The proximal nail plate shows a yellow-white discoloration as presence of fungal elements changes nail plate transparency. Presence of erythema and swelling of proximal and lateral nail folds is common (Fig. 7.1). Inflammation can be prominent in some cases and purulent discharge might occur. Proximal subungual onychomycosis is commonly associated with the following molds: *Fusarium* spp., *Aspergillus* spp., and *Scopulariopsis brevica*ulis [24]. *Fusarium* and *Scopulariopsis brevicaulis* produce a yellow-white discoloration of the proximal nail plate [23, 24], while *Aspergillus* can be associated with a black or green discoloration [25, 26]. The presence of periungual inflammation strongly suggests a mold infection, as this feature is almost never seen in proximal subungual onychomycosis caused by dermatophytes (Fig. 7.2) [5].

Deep white superficial onychomycosis is characterized by opaque, friable, white, superficial lesions that start on the dorsal surface of the nail plate, usually on the toes [26]. Mold infections differ from classic white superficial onychomycosis caused by dermatophytes because the infection is deeper and more diffuse (Fig. 7.3a, b) [27, 29]. Deep white superficial onychomycosis is commonly seen with *Fusarium* spp., *Acremonium* spp., and *Aspergillus* spp. [22, 27, 28].

Distal subungual onychomycosis is primarily a nail bed disorder. Infection usually begins with involvement of the distal part of the nail bed and progresses proximally along the ventral surface of the nail plate. It most commonly affects the great

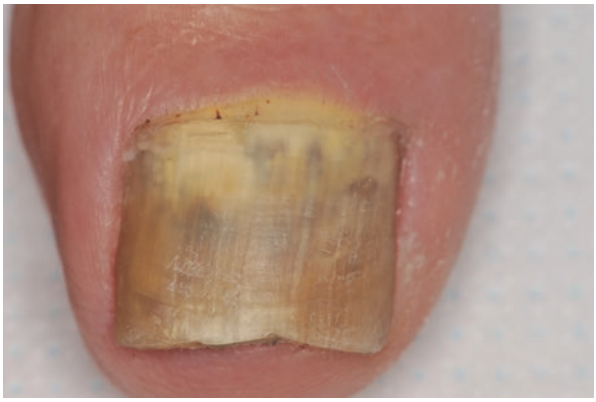

Fig. 7.2 Proximal subungual onychomycosis with periungual inflammation due to *Aspergillus* spp.

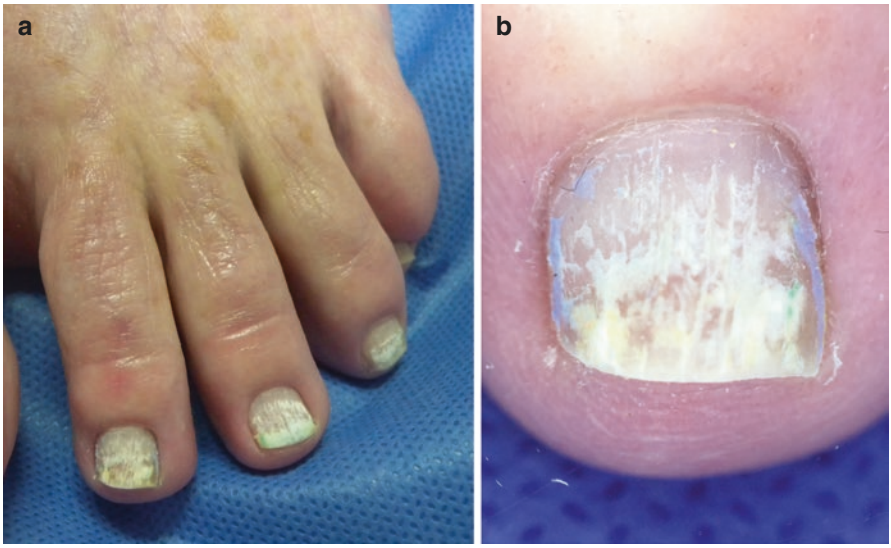

Fig. 7.3 (**a**, **b**) Deep white superficial onychomycosis (**a**) dermoscopy shows invasion of the intermediate nail plate (**b**)

toe [7]. The nails become thick due to subungual hyperkeratosis, which is associated with onycholysis. The onycholytic nail plate is yellowish white to brown in color (Fig. 7.4). Agents responsible for distal subungual onychomycosis include *Acremonium* spp., *Fusarium* spp., and *Alternaria* spp. [5, 7, 8]. Periungual inflammation may be seen in distal subungual onychomycosis caused by *Fusarium* spp. [5]. Tinea pedis is not commonly associated with mold onychomycosis, although it can be seen in *Scopulariopsis brevicaulis* infections.

Pigmented onychomycosis is characterized by a brown or black discoloration of the nail plate due to melanin deposition (Fig. 7.5a, b). Non-dermatophytic molds

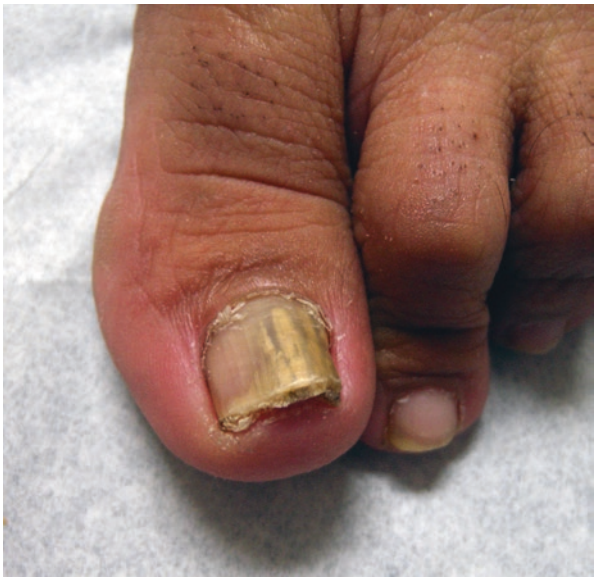

Fig. 7.4 Distal subungual onychomycosis from molds

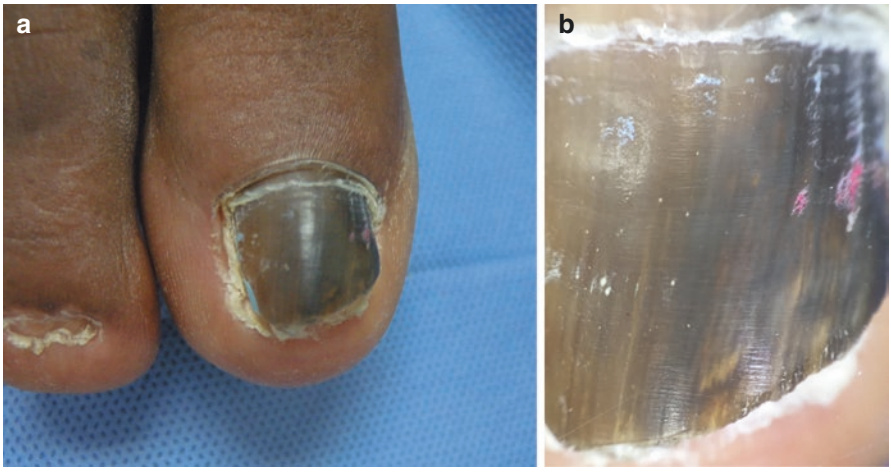

Fig. 7.5 (**a**, **b**) Pigmented distal subungual onychomycosis (**a**) dermoscopy shows yellow-white striae that suggest diagnosis (**b**)

causing pigmented onychomycosis include the dematiaceous fungi *Neoscytalidium dimidiatum*, *Alternaria* spp., and *Exophiala* spp. [7]. These organisms produce melanin, which is incorporated into their cell walls or secreted extracellularly, causing them to appear brown or black when cultured. Pigmented onychomycosis can diffusely affect the entire nail or present as a longitudinal band, mimicking a pigmented lesion (Fig. 7.6) [9]. *Neoscytalidium dimidiatum* can also cause tinea manuum and tinea pedis.

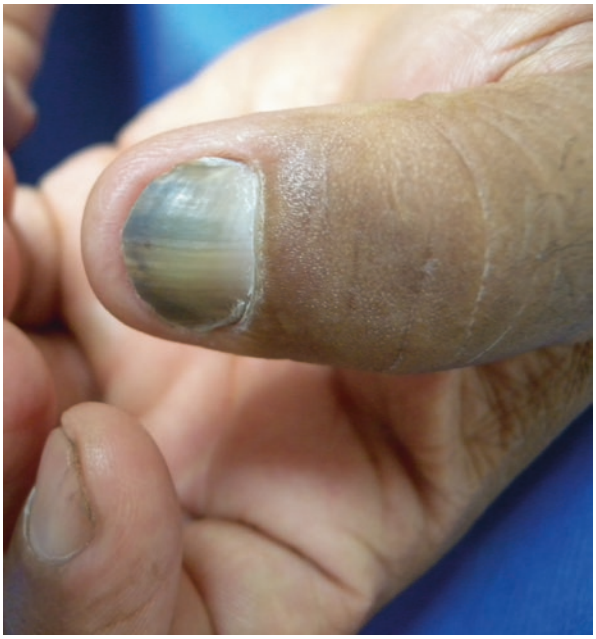

Fig. 7.6 Pigmented onychomycosis mimicking a pigmented lesion

Diagnosis

Nail collection techniques for mycological examination vary depending on the clinical presentation of the mold onychomycosis. In proximal subungual onychomycosis, samples should be obtained from the deep ventral nail plate. This can be easily done using a 3 mm punch or drilling the nail with a scalpel blade. In white superficial onychomycosis, samples are obtained by scraping the affected nail surface [6]. In cases of distal subungual onychomycosis, the sample should include subungual debris from the more proximal part of the lesion. It is very important to alert the lab about possibility of mold infection as dermatophytic media contain factors that inhibit mold growth.

If the physician suspects an infection due to a non-dermatophytic mold, a specimen should be obtained and sent to the mycology lab for confirmatory culture. Pathology of nail clippings does not distinguish between molds and dermatophytes and is not diagnostic in cases of mold infections [10]. Fungal culture mediums generally contain Sabouraud dextrose agar (SDA), along with antibiotics such as gentamicin and chloramphenicol [10, 19] to deter competitive bacterial growth. Non-dermatophytic molds grow faster than dermatophytes and are typically viewed as contaminants in the lab and will grow in SDA along with dermatophytes and yeasts. Cycloheximide is routinely added to the SDA medium in order to inhibit growth of the molds. If a non-dermatophytic mold is suspected, the lab must be

informed that cycloheximide should not be added in order to allow for mold growth and isolation.

Direct microscopic observation does not always result in a positive diagnosis, and one study has shown that more than 42 % of direct microscopic exams were false negatives [1]. Mycologic diagnosis of mold infection requires strict criteria as molds can be common contaminants. The following is considered as "gold standard": microscopic observation of hyphae and/or conidia in 10 % KOH preparations, isolation of the same non-dermatophytic mold in at least three inoculates in two repeated samplings, and failure to isolate a dermatophyte. If a dermatophyte is isolated by culture, there is immediate pathogenic confirmation, unlike the necessary repeated inoculates required to confirm non-dermatophytic mold pathogenesis.

Polymerase chain reaction (PCR) can amplify small fragments of DNA from a fungal biopsy for identification. Fungal species can be identified from the original sample through quantitative PCR, sequencing of PCR amplification products, or restriction fragment length polymorphism digestion analysis [12]. Advantages of PCR include the rapidity and sensitivity, but its use is still limited even though costs are becoming very competitive. This technique cannot distinguish contaminants from pathogens.

Treatment

Treatments of onychomycosis due to non-dermatophytic molds include topical antifungals, systemic antifungals, and chemical nail avulsion.

Non-dermatophytic molds generally do not respond well to systemic therapy, although this is not an absolute. For example, *Fusarium* spp., *Acremonium* spp., *Neoscytalidium* spp., and *Scopulariopsis brevicaulis* rarely respond to systemic medications [23], while *Aspergillus* spp. is sensitive to systemics [5]. Systemic therapy can be given with itraconazole, terbinafine, or fluconazole (not FDA approved for this indication). At times, combinations of systemic, topical, and avulsion treatments may provide the best outcomes for the patient. When systemic therapy is contraindicated, topical agents and/or chemical and surgical avulsion may be used.

Photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) [16] is another treatment modality for distal subungual onychomycosis due to molds. For PDT to be effective against onychomycosis, it is important to remove the nail plate as the photosensitizers need to reach the affected nail bed [13]. This can be achieved using urea ointment [12]. PDT has been established as an effective treatment of non-dermatophytic molds including *Acremonium sclerotigenum* [15].

Summary for the Clinician

- It is important to consider non-dermatophytic molds as causative agents of onychomycosis as rates of infections with these pathogenic agents are increasing.
- Diagnosis of mold infection can only be done by culture or PCR, as fungal stains of nail clippings do not provide discriminatory identification.
- Mold onychomycosis should always be considered in patients presenting with proximal subungual onychomycosis with periungual inflammation, deep white superficial onychomycosis, and pigmented onychomycosis.

Clinical Pearls for the Reader

- Think of molds in cases of proximal subungual onychomycosis associated with erythema and swelling of the proximal/lateral nail folds.
- Think of molds in cases of white superficial onychomycosis that diffusely affect the nail and cannot easily be scraped away.
- Think of molds in cases of pigmented onychomycosis.
- Tinea pedis is not common in association with mold onychomycosis.
- Inform the lab when submitting culture specimens in which you suspect a pathogenic mold.
- Combination of systemic, topical, and podiatric treatments is often required.

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