Chapter 5
Proximal Subungual Onychomycosis

George Glinos and Antonella Tosti

Key Features
- PSO can be caused by *dermatophytes*, *non-dermatophytic molds*, and *Candida* spp.
- PSO due to *dermatophytes* is rare.
- Most often seen in immunocompromised patients (e.g., AIDS, diabetes, transplant recipients).
- *T. rubrum* is the most common cause of infection.
- Infection starts at the proximal nail and progresses distally.

Introduction

Proximal subungual onychomycosis (PSO) is rare. In the traditional classification of this disease, the infection begins with fungal invasion of the proximal nail fold stratum corneum with subsequent infection of the matrix and deeper portions of the ventral nail plate [1–3]. From the proximal nail fold, fungi invade the proximal nail matrix and are incorporated into the newly forming nail, which accounts for the typically slow spread of PSO from the proximal nail fold to the fingertips (Fig. 5.1).

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A. Tosti et al. (eds.), *Onychomycosis*, DOI 10.1007/978-3-319-44853-4_5

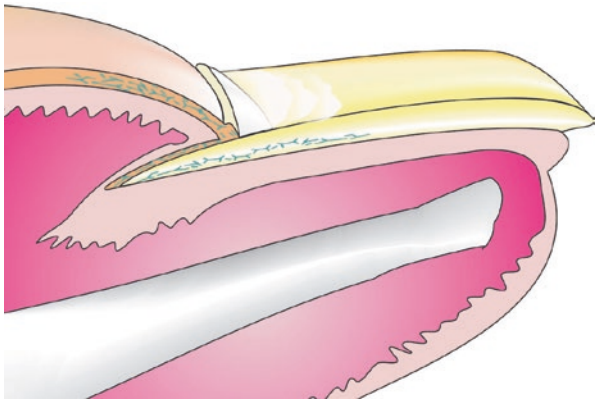

Fig. 5.1 Illustration of the classically described mechanism of pathogenesis in PSO. There is invasion of the proximal nail fold and nail matrix by fungi

Proximal nail plate invasion may occur secondary to acute or chronic paronychia, which is inflammation of the nail fold [4]. This route is most commonly seen with *Candida* [4].

More recently, alternative routes of infection have been described such as hematogenous spread and spread via the lymphatics, which can be exemplified by *maladie dermatophytique* [4, 5]. *Maladie dermatophytique* is a generalized dermatophytosis due to *T. schoenleinii* that affects the skin and internal organs alike [4]. Severe lymphadenopathy is observed in this condition, and biopsies of these enlarged lymph nodes have shown fungal hyphae, which is evidence of systemic spread of the fungal infection via lymphatics [5]. It is now thought that PSO can also be caused by fungal infection of the bloodstream; however, the exact mechanism of transfer from the blood to the nail plate is unclear [4]. Interestingly, there is some new evidence that PSO can progress from an isolated nail infection to a bloodstream infection, especially in immunosuppressed neutropenic patients [4]. The common link between all proposed mechanisms of infection is that fungi gain access to the proximal matrix that produces the ventral nail plate.

The most common organism causing PSO is *Trichophyton rubrum* [6], but many other dermatophytes have been identified such as *T. schoenleinii* [7], *T. megnini* [6, 8], *T. tonsurans* [6, 8], *T. mentagrophytes* [6], *T. epidermophyton* [6], *E. floccosum* [6], and *Microsporum sp.* [9]. Most cases are seen in immunocompromised individuals like HIV/AIDS [6, 8, 10], diabetics, dialysis, and transplant patients [7, 11]. PSO due to dermatophytes is not usually associated with periungual inflammation (Fig. 5.2). Some studies have noted that PSO occurs in up to one third of patients with serious or symptomatic HIV infection and can be considered a sign of immunodeficiency [12]. However, it is important to note that PSO in HIV patients has generally only been studied in those who have progressed to AIDS. Therefore, older data cannot be used to generalize PSO presentation or mycology in all

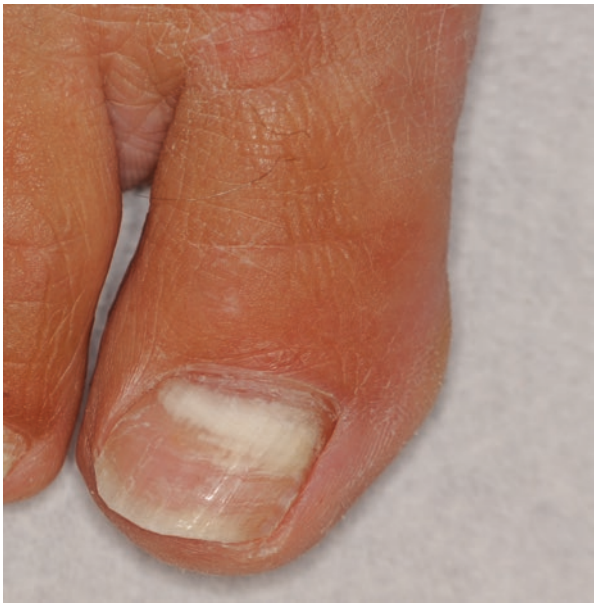

Fig. 5.2 PSO due to *T. rubrum* seen in an immunosuppressed patient

immunosuppressed patients, especially those with higher CD4 counts and without AIDS-defining complications. Moreover, most studies that investigated PSO in AIDS were conducted before the emergence of HAART, which is now the standard of care.

Several non-dermatophytic molds have been identified as causes of PSO including *Fusarium sp.* [13, 14], *Aspergillus fumigatus* [6, 15], *Aspergillus flavus* [16], *Scopulariopsis brevicaulis* [17], and *Acremonium sp*. [17]. Unlike PSO due to dermatophytes, these are not associated with immunosuppressed patients [17]. Non-dermatophytic molds are being increasingly considered a major cause of PSO in otherwise healthy patients. In the original classification of PSO, non-dermatophytic molds were thought to be contaminants, but further investigation has identified them as a significant cause of PSO. Of note, non-dermatophytic PSO is associated with significant periungual inflammation in many cases, which can help distinguish PSO due to dermatophytes from PSO due to non-dermatophytic molds clinically (Fig. 5.3). Distinguishing between dermatophytes and molds is important to guide treatment as their antifungal sensitivities are different.

Lastly, PSO can be caused by *Candida albicans* [6, 18]. *Candida* PSO is usually associated with paronychia, with the assumption that the inflammation can facilitate yeast invasion of the ventral nail plate. *Candida* PSO may rarely occur in chronic mucocutaneous candidiasis (CMCC) [18], a disorder of T cells that is characterized by chronic infection of mucosa, skin, and nails by *Candida*. In CCCA, *Candida* PSO is not always associated with paronychia and patients have a widespread

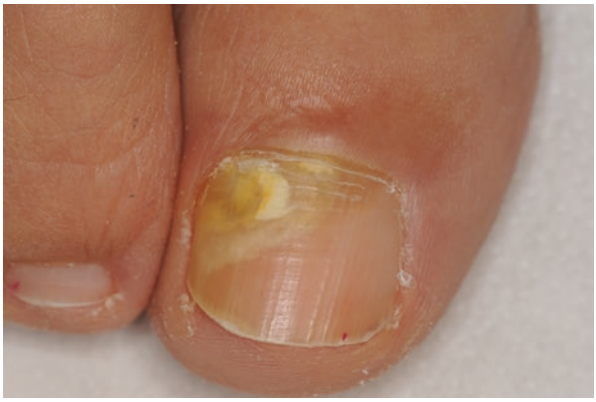

Fig. 5.3 PSO caused by a non-dermatophytic mold

mucocutaneous infection. Of note, the classic nail appearance in CMCC is granulomatous and totally dystrophic. Although PSO is not the most common nail presentation of CMCC, it can certainly be seen in this condition, and it has been reported in more recent literature [18].

Epidemiology

The exact prevalence of PSO is not clear due to a lack of large studies on the subject. Because it is most prevalent in immunocompromised patients, some studies have investigated PSO in this context. A study of onychomycosis in AIDS patients found that 55 of the 62 patients (88.7 %) who were seen for nail infections presented with PSO [6]. They also found that most (83 %) infections occurred in the feet [6]. Because these patients were immunosuppressed, the most common cause of infection were dermatophytes, with *T. rubrum* isolated in 36 (58 %) individuals followed by *T. mentagrophytes* (9.7 %) and *Epidermophyton floccosum* (4.8 %) [6]. Of note, some yeasts were isolated including *Candida albicans* (11.2 %) and *Pityrosporum ovale* (3.2 %) [6]. Of the non-dermatophytic molds, *S. brevicaulis* and *A. fumigatus* were isolated in four patients and one patient, respectively [6]. These non-dermatophytes were found coexisting with dermatophytes and never independently. Incorporating these results and other reports of PSO in the literature, PSO due to dermatophytes can be considered a sign of immunodeficiency [12].

Non-dermatophytic molds are another potential cause of PSO and are the most common cause of PSO in patients who are not immunosuppressed. Mold onychomycosis is not significantly associated with systemic diseases and should not be regarded as a sign of immunodeficiency as PSO due to dermatophytes is. A study at the University of Bologna [17] between 1995 and 1998 identified 59 patients out

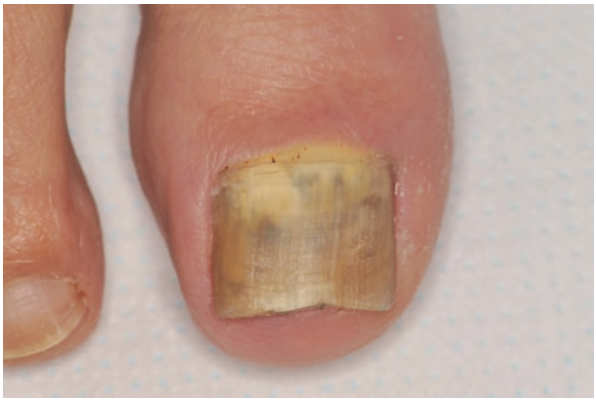

Fig. 5.4 PSO due to mold with associated periungual inflammation

of 1548 who were affected by onychomycosis due to non-dermatophytic molds. Molds were responsible for 13.6 % of all onychomycoses diagnosed via mycology culture, and the majority of these cases (76 %) presented with PSO. *Fusarium* sp. was identified in 44 % of these cases followed by 29 % *Scopulariopsis brevicaulis*, 15 % *Acremonium* sp., and 12 % *Aspergillus* sp. [17].

Furthermore, this study of non-dermatophytic molds identified an interesting relationship between molds and periungual inflammation. The researchers found that all cases of *Fusarium sp.* and *Aspergillus sp*., as well as 59 % of cases of *S. brevicaulis*, were associated with significant periungual inflammation [17]. This contrasts to classic dermatophyte onychomycoses, which were found to almost never cause inflammation [17]. In fact, the authors noted that many of these patients with inflammation were initially treated with antibiotics and anti-inflammatory drugs due to their clinical presentation [17]. Thus, periungual inflammation is an important factor when developing a differential in PSO, and it may help influence what therapy the clinician will recommend (Fig. 5.4).

Generally speaking, the exact prevalence of certain fungi in PSO is unclear. In the past, PSO was thought to originate from periungual inflammation of the proximal nail fold. Also, it was commonly believed that non-dermatophytic molds that were isolated in cases of PSO were contaminants and not the cause of infection [17]. However, it has been revealed in more recent literature that PSO due to molds is frequently associated with periungual inflammation and that molds are a more common cause of PSO than was previously thought, which may invalidate much of our historical data. Furthermore, many of the studies analyzing PSO in the presence of HIV infection were conducted before HAART therapy became the standard of care. Many patients who were studied had extremely low CD4 counts, but today, clinicians can expect to see HIV patients with significantly lower degrees of immunosuppression due to HAART. Thus, one must be careful translating older data into modern clinical practice.

Clinical Features

Proximal subungual onychomycosis (PSO) is an infection of the ventral nail plate. It can be seen in both fingers and toes with the toes being more common. In the classic description of PSO, it begins with fungal invasion of the stratum corneum of proximal nail fold. There is subsequent infection of the deeper portions of the ventral nail plate, which is then followed by slow extension of the infection distally as the nail plate grows [1–3]. Eventually, the infection may involve the entire nail plate [1]. Clinically, this infection appears as a white leukonychia spreading distally as the nail plate grows. PSO causes true leukonychia as the white color is due to lack of light reflection due to the presence of fungi within the nail plate (Fig. 5.5). The nail surface is normal. The leukonychia can originate from the proximal nail fold or from the distal matrix with a single band that follows the shape of the lunula (Figs. 5.6 and 5.7).

Less commonly, the leukonychia can present as alternating transverse bands in which the infection spreads distally from the proximal nail fold in a similar way to the classic presentation, but the infection is remitting and relapsing, which gives the appearance of transverse bands of leukonychia separated by clinically and histologically normal nail plate (Fig. 5.8) [4, 18]. This intermittent dystrophy of the proximal

Fig. 5.5 Dermoscopy of PSO demonstrating true leukonychia. The nail surface is not affected, and the lack of light reflection is due to the presence of fungi within the nail plate

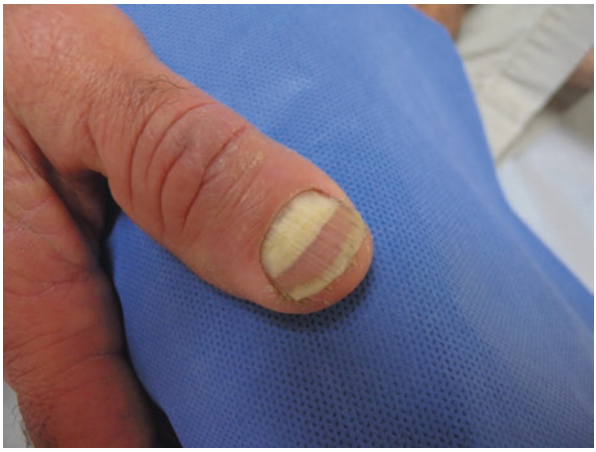

Fig. 5.6 Opaque *white* discoloration of the proximal nail in PSO

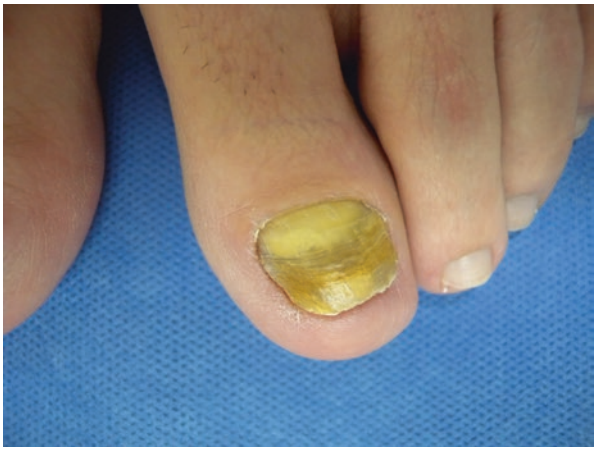

Fig. 5.7 PSO, the nail is dystrophic due to previous avulsions

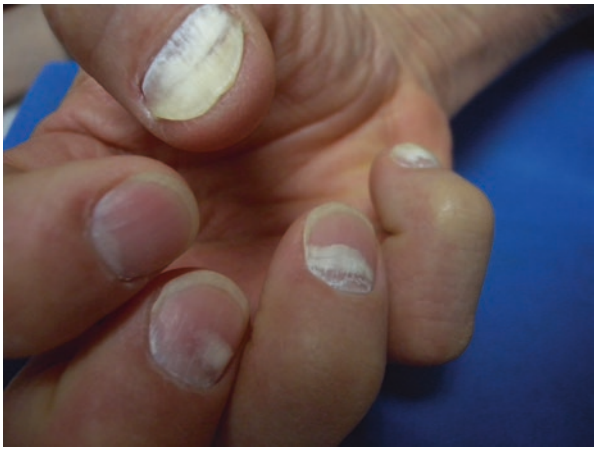

Fig. 5.8 PSO with alternating transverse bands as first described by Baran

nail plate will extend distally to give the appearance of transverse streaks of leukonychia like white waves, either single or multiple. These bands are not due to distal infection but rather proximal nail fold infection for two reasons. First, they have been followed at regular time intervals and are observed to extend distally from the proximal nail fold at a rate consistent with nail plate extension [18]. Second, the unique distal convexity of these transverse leukonychia lesions demonstrates that they are shaped by the lunula [18].

Although it is quite rare, PSO can be due to *Candida* infection. *Candida* usually causes a brownish discoloration of the nails along with severe onychodystrophy [18]. Its presentation can help differentiate it from other causes of PSO, which are mostly associated with white discoloration and milder onychodystrophy. *Candida* PSO is classically seen in those with paronychia and is thought to occur because the inflammation can facilitate yeast invasion to the ventral nail plate. It has also been reported in patients with chronic mucocutaneous candidiasis (CMCC) [18]. In CMCC, PSO due to *Candida* is not always associated with paronychia, and the mechanism of infection in these cases is not clear. Thus, it is important to maintain a high level of suspicion for *Candida* when patients have PSO associated with paronychia but also to appreciate that paronychia is not a defining factor, especially if the patient presents with other mucocutaneous findings.

In regards to symptomatology, patients with PSO may range from being asymptomatic to experiencing pain or discomfort to the degree that it interferes with walking or standing. In PSO due to non-dermatophytic molds, periungual inflammation is especially common and may be quite painful with surrounding erythema and edema. Some cases may even be associated with purulent discharge, which tends to cause these patients to be frequently misdiagnosed as having a bacterial infection.

Diagnostic Clues

PSO should always be considered in the differential diagnosis of true leukonychia.

Diagnosis of fungal infection can be made by visualization of fungal hyphae or fungal elements under direct light microscopy of 20 % potassium hydroxide (KOH) preparation in dimethyl sulfoxide (DMSO). This is the fastest and least expensive option; however, in the case of PSO, it can be challenging to obtain a sample. First, the target site should be cleaned with ethanol to prevent contamination [19]. One must pare the nail plate with a blade to access the ventral side, scraping the white portions of the nail plate, and preparation with KOH will usually reveal abundant hyphal elements under the microscope [1]. Newer techniques such as vertical drilling, horizontal drilling, or subungual curettage have emerged as viable options to obtain samples [20].

The authors like to utilize 3 mm punch to take a big sample that can be divided and utilized for KOH preparation, cultures, and pathology (Fig. 5.9).

Once a sample is obtained, mycological culture should be conducted in addition to other tests using Sabouraud dextrose agar [19]. Littman Oxgall, Borelli medium,

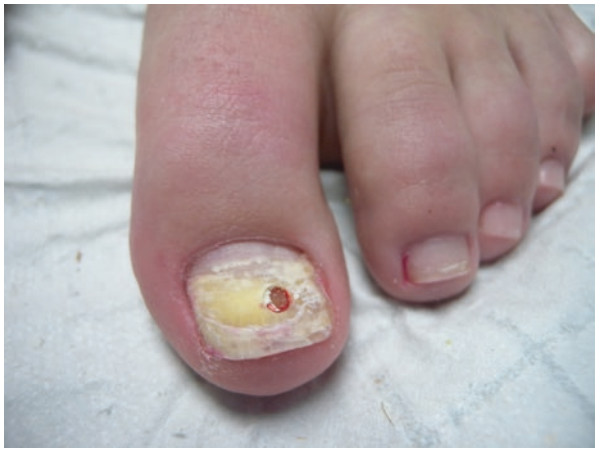

Fig. 5.9 Sample can be taken with a 3 mm punch biopsy for histopathological analysis

or potato dextrose agar may also be used. The samples must be incubated at 26–30 °C for several weeks to 1 month. It is important to select agar without cycloheximide, which is a common additive. Cycloheximide is added to inhibit the growth of non-dermatophytic molds, but we now know these are an important cause of PSO [19]. When a mold is suspected, it is recommended to serially sample the patient's nails at different points of time to confirm the repeated presence of non-dermatophytic mold to ensure that the non-dermatophytic mold is part of the primary infection and not a contaminant [19]. Fungi are notoriously difficult to culture. Not only does this method of diagnosis take a long time, but sensitivity and specificity is limited by fungal viability on the chosen medium as well as sampling technique.

On histopathology, nail samples are stained with periodic acid-Schiff (PAS) or grocott's methenamine silver (GMS). With the PAS technique, the fungi are stained magenta, but it only works on living fungi. With the GMS technique, the fungi are stained dark brown on a background of pale green, and it works for both living and dead fungi. As with other techniques, it is key to identify fungi in the ventral nail plate. This method has high sensitivity and specificity, especially in the hands of an experienced histopathologist.

In the current literature, several studies have investigated the applicability of these various diagnostic techniques. Generally, histopathological examination with PAS staining (HPE-PAS) is found to have the highest positive predictive value and negative predictive value and is regarded as the gold standard for diagnosis of onychomycosis [21, 22]. However, not many studies have focused on comparing diagnostic methods in PSO specifically. It can be assumed that these diagnostic tests may have similar predictive value in PSO, but that cannot be known with certainty at this time.

Lastly, newer PCR techniques have been introduced for the diagnosis of onychomycoses and offer some advantages over traditional diagnostic methods [23]. PCR provides a much faster diagnosis within days versus weeks with traditional culture. Also, it has less vulnerable errors due to contamination, fungal viability, or sampling technique [23].

The key to making any diagnosis of PSO is to sample the ventral nail plate. Diagnosis may be difficult due to its atypical clinical presentation, but always maintain an appropriate level of suspicion when a patient displays one of the presentations noted earlier in this chapter.

Summary for the Clinician

Proximal subungual onychomycosis (PSO) is an infection of the proximal ventral nail plate. It can be due to dermatophytes, non-dermatophytic molds, or *Candida*. PSO due to dermatophytes is rare and is most frequently found in patients with suppressed immune systems, especially HIV/AIDS, or in patients taking systemic immunosuppressors. The most common agent in these cases is *Trichophyton rubrum*, but other dermatophytes have also been implicated. Non-dermatophytic molds have emerged as a more common cause of PSO than previously thought. These cases are not associated with immunosuppression and are often associated with significant periungual inflammation. Less commonly, yeasts like *Candida* can be the causal pathogen. Classically, PSO is seen as a white patch in proximal nail plate and extending distally as the nail grows; however, other less common presentations like alternating transverse bands have been described. It can be diagnosed by KOH prep microscopy, histopathologic analysis, culture, and PCR. Obtaining an adequate sample of the ventral nail plate is key to diagnosis.

Clinical Pearls

- Maintain a high level of suspicion for PSO in immunosuppressed patients with proximal nail leukonychia.
- Think of molds in case of PSO associated with periungual inflammation.
- A 3 mm punch can be utilized to obtain a sample from the ventral nail plate.
- PSO requires systemic treatment.

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