Objective: To analyze the epidemiology, responsible agents, clinical features, and outcome of white superficial onychomycosis (WSO).

Design: Retrospective study.

Setting: University hospital.

Patients: A total of 79 patients with WSO seen at the Department of Dermatology of Bologna University from 1994 to 2002. Responsible agents included *Trichophyton interdigitale* in 58 cases (73%), *Trichophyton rubrum* in 4 (5%), *Fusarium* species in 9 (11%), *Aspergillus* species in 5 (6%), and *Acremonium strictum* in 3 (3%).

Results: White superficial onychomycosis may have different clinical and epidemiological features. “Classic” WSO, characterized by superficial nail plate involvement, is usually due to *Trichophyton mentagrophytes* (var *interdigitale*), although *Acremonium strictum* or *Onychocola canadensis* can sometimes be responsible. A deep and diffuse WSO, characterized by massive penetration of the nail plate by fungi, can be seen in nail infections by molds such as *Fusarium* species and *Aspergillus* species, or in nail infections by *Trichophyton rubrum* in healthy children and in patients infected with human immunodeficiency virus.

Conclusions: Severity and spread of WSO is the result of complex host-parasite relationships. When dealing with a patient with WSO, we should always consider the causative organism and the host characteristics to choose the best therapeutic approach.

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Table 1. Fungi Responsible for White Superficial Onychomycosis in a Study of 79 Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Trichophyton interdigitale</th>
<th>Trichophyton rubrum</th>
<th>Fusarium Species</th>
<th>Aspergillus Species</th>
<th>Acremonium strictum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>67 (45-96)</td>
<td>23 (7-43)</td>
<td>3 with F solani 6 with F oxysporum</td>
<td>2 with A candidus 3 with A terreus</td>
<td>3</td>
</tr>
<tr>
<td>Predisposing factors (No. of patients)</td>
<td>Tinea pedis (23)</td>
<td>HIV infection (2), tinea pedis (3), affected family member (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected fingers, No. (No. of patients)</td>
<td>1 (36), &gt;1 (21)</td>
<td>1 (2), 2 (2)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Patients cured by topical treatment, No.</td>
<td>57/57</td>
<td>2/4</td>
<td>6/9</td>
<td>2/5</td>
<td>3/3</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable.

From 1994 to 2002 we diagnosed 79 cases (in 44 men and 35 women) of WSO. Of these, 58 (73%) were due to *Trichophyton interdigitale*, 4 (5%) to *Trichophyton rubrum*, 9 (11%) to *Fusarium* species, 5 (6%) to *Aspergillus* species, and 3 (3%) to *Acremonium strictum*. Details about the patients are listed in Table 1. The 19 cases of clinically evident WSO with negative cultures that were seen in the same period were not included in this review.

*Trichophyton interdigitale* was responsible for WSO in 58 patients, all adults. Predisposing factors included tinea pedis (both plantar and interdigital) caused by *Trichophyton interdigitale*. Twenty five of these patients also had a distal subungual onychomycosis (DSO) due to *Trichophyton interdigitale* (7 cases) or to *Trichophyton rubrum* (18 cases) in the same or in other nails. White superficial onychomycosis due to *Trichophyton interdigitale* always involved the toenails, usually the first, and presented as 1 to 5 small whitish opaque friable patches on the nail (Figure 1). Scraping these patches permitted the removal of the whitish surface material, exposing a transparent compact median nail plate. In 2 cases, histopathologic examination revealed chains of small spores and hyphae in splits in the dorsal nail and on the nail surface. The intermediate and the ventral nail were spared. The mechanical removal of the affected nail plate, followed by applications of topical antifungal agents, produced a clinical and mycological cure in all patients.

*Trichophyton rubrum* was isolated in 4 patients, 2 HIV-positive adults and 2 healthy children. Both of the HIV-positive patients had a plantar tinea pedis due to *Trichophyton rubrum*. A plantar tinea pedis due to *Tricho-

phyton rubrum* was also diagnosed in 1 of the children, a 10-year-old boy whose father had a distal subungual onychomycosis of the toenails due to *Trichophyton rubrum*. Clinically, WSO presented with diffuse nail plate involvement in all 4 patients. The affected nail (usually 1 or both great toenails) was diffusely milky white and opaque, and the discoloration reached the proximal nail fold (Figure 2 and Figure 3). Mechanical scraping removed a thick layer of the plate, suggesting a deep penetration of fungi within the nail plate. However, the deeper portion of the nail was spared. Topical treatment with amorolfine nail lacquer produced complete cure of the onychomycosis in the 2 children within 6 months. In the 2 patients with HIV, periodic removal of the whitish plate followed by applications of topical antifungals only produced improvement of WSO, which was still present after 1 year of treatment.

Nondermatophytic molds were responsible for 17 cases of WSO: *Fusarium* species (*Fusarium solani* and *Fusarium oxysporum*) in 9 cases, *Aspergillus* species (*Aspergillus candidus* and *Aspergillus terreus*) in 5, and *Acremonium strictum* in 3. These patients were healthy adults with no associated cutaneous mycoses, and none was used to walking barefoot in the grass. Clinically, *Acremonium strictum* WSO was indistinguishable from *Trichophyton interdigitale* WSO, and *Fusarium* species WSO and *Aspergillus* species WSO presented with a total nail plate...
involvement (Figure 4). The affected nail, always a toenail, usually the first, was opaque, friable, with a diffuse white pigmentation and yellow-brown patches. Nail plate discoloration extended to the proximal nail fold, and the pigmentation was visible through the cuticle. In 8 patients the proximal nail fold was mildly inflamed. Scraping of the affected nail plate permitted easy removal of a thick portion of the nail that was friable and soft. The deep layers of the nail plate were, however, intact. A punch biopsy specimen obtained in 1 patient with *Fusarium solani* WSO showed short, branched filaments in splits in the nail plate that went deep of the nail plate. All 3 patients with *Acremonium strictum* WSO were cured by topical treatment with antifungics. Eight of the 14 patients with *Fusarium* species (6 cases) or *Aspergillus* species (2 cases) WSO were cured by periodic mechanical removal of the affected nail plate followed by application of antifungal nail lacquers (either ciclopirox or amorolfine). In 6 patients with *Aspergillus* or *Fusarium* WSO, systemic antifungals were added to the treatment. Itraconazole (400 mg/d 1 week per month) induced clinical and mycologic cure in 1 patient with *Aspergillus candidus* WSO and 1 patient with *Fusarium solani* WSO after 6 and 8 months of treatment, respectively. Terbinafine (250 mg/d) cured 1 patient with *Aspergillus terreus* WSO and 1 with *Fusarium solani* WSO after 6 months of treatment. No recurrences were seen in patients with mold WSO after successful treatment.

Two patients with diffuse WSO (1 due to *Fusarium solani* and 1 due to *Aspergillus terreus*) were not cured by either itraconazole or terbinafine in association with the topical treatment.

**COMMENT**

On the basis of our data and a review of the literature, we can divide patients with WSO into 4 groups characterized by different epidemiological and clinical features (Table 2).

**CLASSIC WSO DUE TO DERMATOPHYTES IN HEALTHY PEOPLE**

First described by Zaias in 1966,3 this variety is usually due to *Trichophyton interdigitale* (in more than 90% of cases), although in some cases it is due to *Trichophyton rubrum*, and, rarely, to other dermatophytes.4,5 White superficial onychomycosis typically affects 1 or more toenails, most commonly the first, second, and third. Interdigital tinea pedis (or rarely, plantar tinea pedis) due to *Trichophyton interdigitale* is often associated. Involvement of the fingernails has rarely been described in adults.6

Clinically, WSO presents as 1 or more white, opaque, scaly plaques with distinct edges localized on the dorsal surface of the nail plate, each plaque corresponding to a dermatophyte colony.7 Because of the minimal nail plate penetration, the plaques are easily scraped away with gentle curetting.

Histopathologic examination with periodic acid–Schiff stain reveals small islands of chains of small spores and short hyphae in splits in the nail surface and in the superficial layers of the nail plate.8 Fungi have a saprophytic rather than parasitic morphology. They form not true hyphae but modified hyphal structures with various shapes, termed eroding fronds, perforating organs, and carpel bodies.9 These hyphal elements enable fungi to penetrate hard, keratinized structures and they have also been described in hair, feather, and horn.10

Dermatophytes cause WSO when they possess keratinolytic enzymes able to metabolize the hard keratins of the superficial nail plate. Studies in vitro have shown that *Trichophyton interdigitale* has a high osmotolerance
that may increase its ability to invade the relatively dry dorsal surface of the nail plate.\textsuperscript{11} The rare cases of \textit{Trichophyton rubrum} WSO reported in healthy people may have been favored by nail plate occlusion caused by an over-riding toe.\textsuperscript{12}

The prevalence of WSO in the general population is estimated to be approximately 1% to 2%,\textsuperscript{13} and the incidence increases with age.\textsuperscript{14} In a survey of onychomycosis in the elderly, we found that 4% of the Italian population older than 65 years is affected by WSO.\textsuperscript{15} White superficial onychomycosis due to \textit{Trichophyton interdigitale} accounted for 5.8% of all onychomycoses diagnosed at our practice for nail disorders from 1994 to 2002. An associated DSO may be present, not necessarily due to the same fungus.\textsuperscript{13,15}

Treatment of this type of WSO consists of the mechanical removal of the whitish plaque, followed by applications of topical antifungal agents until clinical and mycologic cure, usually achieved after 6 months. In our experience, antifungal agents are effective in both creams and nail lacquers.

**MOLD WSO**

Several nondermatophyte molds are known to be able to invade the superficial nail plate.\textsuperscript{9} The most common are \textit{Fusarium} species, \textit{Aspergillus} species, and \textit{Acremonium} species.

Mold WSO usually affects a single toenail, mainly the first in adults. Patients sometimes report barefoot gardening, suggesting a possible contact with the fungi via the soil.

Clinically, mold WSO may be indistinguishable from dermatophyte WSO or it may show a diffuse involvement of the nail both in width and depth. This is especially seen in \textit{Fusarium} and \textit{Aspergillus} WSO.\textsuperscript{10} In these cases, the nail is diffusely opaque, friable, with a pigmentation varying from homogeneously white to patchy yellow brown. The color of the pigmentation may result from the production of pigmented conidia within the nail. Nail plate discoloration involves the entire nail surface and often extends beneath the proximal nail fold; in this case, the pigmentation is visible through the cuticle.

Mechanical removal of the invaded nail plate reveals deep penetration of hyphae that may sometimes even reach the ventral portion of the nail. Progression is usually rapid and patients often complain that the entire nail has become pigmented in a few months. As seen in the other types of onychomycoses due to nondermatophyte molds,\textsuperscript{2} periungual inflammation is commonly associated, usually without pus discharge. Pigmentation of the proximal nail and deep invasion of the nail plate often makes it difficult to distinguish between WSO and a proximal subungual onychomycosis (PSO) due to molds.\textsuperscript{3} Histologically, mold WSO is characterized by the presence of short-branched filaments in splits in the nail plate that are easily scraped away.

The prevalence of mold WSO is not known. According to Zaias,\textsuperscript{9} 5% of all WSOs are due to nondermatophyte molds,\textsuperscript{2} and there is no association with tinea pedis, which suggests that host factors play no role in its development. \textit{Acremonium strictum} and \textit{Onychocola canadensis} may also, but rarely, be responsible for a classic WSO. \textit{Scytalidium dimidiatum} may cause a superficial black onychomycosis characterized by small, opaque black patches on the dorsal nail plate that are easily scraped away.

The prevalence of mold WSO is not known. According to Zaias,\textsuperscript{9} 5% of all WSOs are due to nondermatophyte molds. In our series, 21% of the cases were due to nondermatophytes. This high prevalence, however, may only be apparent, as the severity of WSO due to molds prompts patients to ask for dermatologic advice. Moreover, mold WSO seems to affect patients younger than those with \textit{Trichophyton interdigitale} WSO, and young patients are more bothered by the rough black nails than the elderly. Mold WSO affects healthy adult patients and is not associated with tinea pedis, which suggests that host factors play no role in its development. \textit{Acremonium strictum} and \textit{Onychocola canadensis} WSOs are usually cured by mechanical removal of the affected nail plate followed by applications of topical antifungals. Treatment of deep and diffuse WSO due to \textit{Aspergillus} and \textit{Fusarium} is more difficult since the nail is invaded in its deepest portion. Repeated mechanical removal of the invaded plate is advisable. Systemic antifungals may be necessary in recalcitrant cases that do not benefit from topical treatment. In our experience, most cases of \textit{Aspergillus} and \textit{Fusarium} WSO can be treated with either systemic terbinafine at the dosage of 250 mg/d for 6 months or systemic itraconazole at the dosage of 400 mg/d.
1 week per month for 6 months, in association with weekly applications of antifungal nail lacquers.

**CHILDHOOD WSO**

Dermatophyte WSO can be observed in prepubertal children, in whom it is due to *Trichophyton rubrum*. Clinically, WSO in children may present as a classic WSO or, more frequently, may show diffuse invasion of the nail plate. In these cases the nail appears homogeneously white, opaque, and friable, with clinical features resembling a PSO extending to the superficial nail plate. The involvement of the entire thickness of the nail plate in children WSO may be explained by the thinness of their nail plate. In 1 of our 2 children and in 6 of the 7 cases of children reported by Ploysangam and Lucky, WSO was associated with tinea pedis due to *Trichophyton rubrum*. A family history of tinea pedis or *Trichophyton rubrum* onychomycosis is also common in these patients, which suggests a genetic susceptibility to dermatophyte infection contracted in the familial environment. Topical treatment was successful in our 2 children with WSO and in 1 of the 4 patients followed up by Ploysangam and Lucky, while in the other 3 children of their series WSO was only improved by therapy.

Diffuse *Candida* species WSO of several fingernails and toenails may be seen in premature infants born to mothers with vaginal candidiasis. Oral candidiasis (thrush and angular cheilitis) is often associated. Clinically, the nail plate is opaque and diffusely milky white. The clinical features resemble a PSO extended to the entire nail plate, and histopathologic studies show almost total nail plate invasion by *Candida*. Contamination during delivery is the source of the infection, which often resolves spontaneously after a few months, as soon as the immune system is completely developed.

**WSO IN HIV-POSITIVE INDIVIDUALS**

Up to 30% of patients with HIV infection have onychomycosis. All varieties of onychomycosis are more frequent in HIV-positive individuals than in controls and their frequency is related to the patient’s degree of immunodepression. Onychomycosis is most likely to develop when the CD4 cell count drops to approximately 450/µL.

A recent study has shown a prevalence of WSO of 9.5% in HIV-infected patients. In a further 15% to 50% of these patients, WSO was associated with DSO. In HIV-infected patients, WSO is usually due to *Trichophyton rubrum* and is not only seen in the toenails but can also affect the fingernails.

Clinically, the affected nail appears diffusely opaque and white, and the pigmentation often reaches the proximal portion of the nail. It is therefore often difficult to discriminate between a WSO that has extended deeply and a PSO that has extended superficially.

A case of WSO due to *Trichophyton rubrum* has been described in a young child with HIV infection whose parents both had tinea pedis and/or onychomycosis due to *Trichophyton rubrum*. Clinically, WSO involved the nail plate diffusely, resembling a PSO that had extended superficially in a thin nail plate. Immunodepression was the predisposing factor in this patient who had acquired the fungus from the familial environment.

A case of *Trichophyton rubrum* WSO resembling a PSO extended superficially has been also described in a patient with graft-vs-host disease.

Our 2 HIV-infected patients with *Trichophyton rubrum* WSO were not cured by topical treatment, suggesting that a systemic treatment may be necessary in these cases.

Besides the classic WSO of healthy adults, usually due to *Trichophyton interdigitale*, there are other subtypes of WSO with distinctive clinical or epidemiological features. The most striking characteristic of these forms is the deep invasion of the nail plate. It can be seen in WSO due to molds such as *Aspergillus* species and *Fusarium* species, in WSO due to *Trichophyton rubrum* in children or *Candida* in newborns, and WSO due to *Trichophyton rubrum* in adults and children with HIV infection.

The severity and extension of mycotic infections are the result of complex host-parasite relationships and WSO does not seem an exception to this rule. The presence of penetrating organs enables the parasites to invade the nail plate and progress deeply. Host factors that may be important in favoring severity of WSO include decreased immune function, genetic factors, and local factors such as nail plate thickness.

In *Aspergillus* and *Fusarium* WSOs, the extent of nail invasion is strictly related to the fungi’s ability to penetrate the keratinized nail plate. Host characteristics do not seem to play a role, since mold WSO typically affects healthy people with previously healthy toenails.

Children may have a deep WSO for both physiological and pathological reasons. White superficial onychomycosis due to *Candida* is typical of premature newborns with a transient immunological deficit against the yeast. In healthy children *Trichophyton rubrum* WSO may be facilitated by a genetic predisposition to the infection and by family members with the same disease. Like DSO, WSO can also be considered an autosomal dominant disease, where genetic predisposition makes the nail surface poorly resistant to fungal penetration. All cases of childhood WSO reported in the literature are due to *Trichophyton rubrum*. This may be due to the low number of reports or may be proof that they are examples of familial *Trichophyton rubrum* infection. The physiological fact that children’s nails are very thin makes it easier for the fungus to invade the entire thickness of the nail plate.

Patients with HIV infection may have a *Trichophyton rubrum* WSO that progresses deeply, resulting in a clinical picture of a mixed WSO/PSO. A deficient immune response against the fungus secondary to HIV infection is probably involved. Since HIV infection decreases nail resistance to ordinary pathogens, the avascular nail plate may in some way be affected by low CD4 cell count. Moreover, the deficient immune response of HIV-infected patients also predisposes them to *Trichophyton rubrum* colonization of the skin of the plantar or interdigital areas, which provides a fungal reservoir for nail invasion.

Since it is established that it can progress deeply and involve the nail extensively, WSO should no longer be
considered a superficial variety of onychomycosis. As with DSO and PSO, WSO can progress to invade the whole nail and cause total dystrophic onychomycosis. Some cases of white total dystrophic onychomycosis may actually derive from a WSO.

When dealing with a patient with WSO, we should always consider the causative organism and the host characteristics to choose the best approach. Scraping the superficial nail plate, together with applications of a topical antifungal agent, is the treatment of choice for WSO due to *Trichophyton interdigitale* in healthy adults. In children, a simple topical treatment with nail lacquers may be tried, even in the case of diffuse nail involvement, because the thin nail plate of children may easily be penetrated by drugs. In the other forms of WSO, a combination of systemic and topical antifungals and the periodic removal of the affected nail plate is the treatment of choice.

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REFERENCES