CLINICAL MICROBIOLOGY REVIEWS, July 1998, p. 415–429 Vol. 11, No. 3
0893-8512/98/$04.00+0

Onychomycosis: Pathogenesis, Diagnosis, and Management

BONI E. ELEWSKI*

Department of Dermatology, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio

INTRODUCTION

Most cutaneous infections are the work of the homogeneous group of keratinophilic fungi known as dermatophytes. The dermatophyte *Trichophyton rubrum* is the major cause of tinea pedis and onychomycosis (8). After originating in West Africa, Southeast Asia, Indonesia, and Northern Australia, *T. rubrum* spread to Europe and North and South America in the late 19th and early 20th centuries, where it found a niche within a recently shod populace (8). Subsequent 20th century developments including wars, the modern health movement and the associated use of occlusive footwear and locker rooms, and migration of people since the invention of the jumbo jet, promoted an increased incidence of tinea pedis and onychomycosis (8).

Dermatophytoses of the fingernails and toenails, in contrast to those at other body sites, are particularly difficult to eradicate with drug treatment. This is the consequence of factors intrinsic to the nail—the hard, protective nail plate, sequestration of pathogens between the nail bed and plate, and slow growth of the nail—as well as of the relatively poor efficacy of the early pharmacologic agents.

Recent years, however, have witnessed the development of a

* Mailing address: Department of Dermatology, University Hospitals of Cleveland, 11100 Euclid Ave., Cleveland, OH 44106-5028. Phone: (216) 844-3177. Fax: (216) 844-8993. E-mail: BEELEWSKI@AOL.COM.

new generation of antifungal drugs that produce impressive, long-lasting cure rates with shorter treatment times and better safety profiles than ketoconazole and griseofulvin. In this paper, current knowledge of the pathogenesis, diagnosis, and management of onychomycosis with these new agents is reviewed and evaluated.

ONYCHOMYCOSIS

Definition and Clinical Impact

"Onychomycosis" traditionally referred to a nondermatophytic infection of the nail but is now used as a general term to denote any fungal nail infection (63) (tinea unguium specifically describes a dermatophytic invasion of the nail plate). In spite of the clearly diseased appearance associated with this condition, onychomycosis is all too often regarded as merely a cosmetic problem of relatively minor importance that is hardly worth the effort to resolve. This belief may have been supported by the adverse effects and long dosing courses associated with some of the earlier antifungal agents.

In fact, onychomycosis can have significant negative effects on patients' emotional, social, and occupational functioning and can, in addition, consume a sizable proportion of health care dollars. Affected patients may experience embarrassment in social and work situations, where they feel blighted or unclean, unwilling to allow their hands or feet to be seen. Patients may fear that they will transmit their infection to family members, friends, or coworkers, fears that can lead to diminished self-esteem and the avoidance of close relationships (55). Employment suffers if employers are reluctant to hire individuals with abnormal nails, particularly for jobs such as food handling or modelling or where interaction with the public is required. A more tangible barrier to work success is the discomfort some patients experience that prevents them from carrying out work-related tasks such as prolonged standing, writing, or typing. Finally, onychomycosis can compel workers to take periodic sick leave, a problem even for treated patients if therapy is ineffective and/or long-lasting (55). This lack of success, in turn, can cause patients to feel discouraged or even to stop treatment, resigning themselves to permanent disfigurement and discomfort.

Onychomycosis in immunocompromised patients, such as those infected with human immunodeficiency virus (HIV), can pose a more serious health problem (55). Not only does the difficult-to-treat infection serve as a constant reminder to the patient of his or her own deteriorated condition, but the possibility exists of transfer of a very high titer of fungal pathogens to another person (55).

Epidemiology and Risk Factors

Dermatophytoses of the stratum corneum, hair, and nails are common, whereas infection of the dermis and subcutaneous tissue by these agents is rare (64). Although dermatophytic infections are rarely life-threatening, their high incidence and prevalence and the associated morbidity (64) make them an important public health problem (1).

Reports concerning the prevalence of onychomycosis are conflicting, with estimates ranging from 2 to 3% of the general U.S. population (27) to 13% of the male Finnish population (40). In a recent outpatient-based, cross-sectional survey of 1,038 patients in a dermatology clinic waiting room in Cleveland, Ohio, culture-confirmed dermatophyte onychomycosis was identified in 8.7% of the total population and in 6.5 and 13.3% of the female and male subgroups, respectively (patients who presented for onychomycosis were excluded) (27). These figures are comparable to those for the general Finnish population (8.4%) (40). Several studies have shown that the prevalence of onychomycosis increases with age. For example, none of the 200 Finnish subjects who were younger than 20 years had onychomycosis but almost 24% of those aged 70 years or older had the disorder. Similarly, 28.1% of the members of the Ohio cohort aged 60 years or older were culture positive for onychomycosis, versus 1.1 and 2.9% for those aged 10 to 18 years and 19 to 30 years, respectively (27). Reasons for the age-related increase in onychomycosis may include poor peripheral circulation, diabetes, repeated nail trauma, longer exposure to pathogenic fungi, suboptimal immune function, inactivity, or the inability to cut the toenails or maintain good foot care (22, 27, 55).

As is the case among adults, prevalence rates for onychomycosis among children are quite variable: a recent review of studies of the subject in several countries outside North America lists prevalence rates varying from 0% (United States, Wales, and Finland) to 2.6% (Guatemala) (38). To learn more about the prevalence of onychomycosis among children in North America, a prospective survey was conducted of 2,500 young (≤18 years) patients and family members in Canada and the United States. Subjects' nails were examined for signs of onychomycosis and sampled for direct microscopy and culture. Onychomycosis was diagnosed in 11 children (10 with affected toenails, and 1 with affected fingernails), indicating a prevalence of 0.44%; however, 7 of these children had been referred for treatment of onychomycosis or tinea pedis. Thus, the prevalence of onychomycosis in children with primary diagnoses other than onychomycosis or tinea pedis was 4 of 2,500, or 0.16% (37). The reasons for this 30-fold decrease in the prevalence of onychomycosis in children relative to adults may include reduced exposure to fungus because less time is spent in environments containing pathogens; faster nail growth; smaller nail surface for invasion; and lower prevalence of tinea pedis (37).

Contact with the source of the infection constitutes a risk factor; for example, *Trichophyton verrucosum* commonly infects the faces of farmers who lean against their cows as they milk them (64). There is no doubt that several factors unique to modern life have resulted in an increased prevalence of onychomycosis. These include the wearing of shoes, particularly fashionably tight, high-heeled shoes; the increased use by large numbers of people of damp spaces such as locker rooms and gymnasiums; the declining health of the aging American population, and the increased number of immunocompromised patients through disease (e.g., HIV infection) or therapeutic agents (e.g., immunosuppressive therapies associated with cancer or posttransplantation care, and the extensive use of broad-spectrum antibiotics) (25). Other factors that increase the risk of onychomycosis are direct trauma to the nail, including that resulting from certain tic disorders (e.g., nail biting).

DERMATOPHYTES AND ONYCHOMYCOSIS

The term "dermatophytosis" is used to describe infection by members of the genera *Microsporum*, *Trichophyton*, and *Epidermophyton*. The species that most often cause onychomycosis in North America and parts of Europe are *T. rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*: the first two species are much more often implicated than *E. floccosum* (58). Infections of the skin, nail, and hair by nondermatophytic molds such as *Scytalidium* and *Scopulariopsis* are termed "dermatomycoses." Dermatophytes account for most (90%) cases of onychomycosis of the toenails and at least 50% of fingernail

infections (31). Both dermatophytes and nondermatophytes, especially *Candida albicans*, have been identified as sole etiologic agents of onychomycosis; however, the incidence of true mixed infections (caused by dermatophytes plus nondermatophytes) is difficult to determine accurately (58) and is discussed in detail below.

The dermatophytes are hyaline septated molds. The hyphae of these mycelial organisms penetrate the stratum corneum of the skin and nails. The fungal cells manufacture keratinolytic proteases, which provide a means of entry into living cells (39). Some dermatophytic species, which are basically soil saprophytes that have acquired the ability to digest keratinous debris in soil, have evolved to be capable of parasitizing keratinous tissues of animals (1).

The families that include many of the known keratinolytic fungi are the *Arthrodermataceae* and *Onygenaceae* in the phylum *Ascomycota* (52). Members of these families are homogeneous with respect to appearance, physiology, taxonomy, antigenicity, basic growth requirements, infectivity, and the diseases they cause (52). Some, such as *Microsporum canis* and *T. mentagrophytes*, have affinity for the keratin of animals and humans, whereas others are more specialized for a particular animal host (1).

Variability with respect to the causative microorganism is both geographic and, within a given region, temporal. Because organisms that cause clinically apparent disease tend to receive the most attention, pathogens whose invasion leads to hard-to-detect disease may be present in a region but are less likely to be identified (1). By contrast, pathogens that cause readily apparent signs and symptoms are likely to be identified and their prevalence is likely to be noted. Thus, because reports during the 1970s focused primarily on scalp infections, *T. violaceum* was the most frequently isolated dermatophyte during that decade in Europe (1) although *T. tonsurans* is the principal agent of tinea capitis in the United States and is emerging in Europe.

Changes over time within a region in the prevalence of particular dermatophyte species also are common: although *M. audouinii* and *M. canis* were the most common causes of scalp infection in Western and Mediterranean Europe 50 to 100 years ago, tinea capitis has declined in incidence in Western Europe and, when present, is caused primarily by *M. canis* (1) or *T. violaceum* (1). Similarly, *M. audouinii* and *M. canis* were the main causes of tinea capitis in the United States earlier in this century; this role has been taken over by *T. tonsurans* (1). Another change that has occurred in recent years is the growing prevalence of dermatophytoses of the foot (tinea pedis) and nails (tinea unguium) and decline in the prevalence of scalp infections (1).

CLINICAL TERMINOLOGY

As in many areas of medicine, the clinical terminology used to describe dermatophytic infections evolved in advance of accurate knowledge about causation or pathophysiology. Tinea ("a gnawing worm") or "ringworm," a term derived from the appearance of the characteristic skin lesions in this common dermatophytosis (64), affects the scalp (tinea capitis), glabrous skin (tinea corporis), groin (tinea cruris), nail (tinea unguium), feet (tinea pedis), beard (tinea barbae), and hand (tinea manuum). Other dermatophytoses are named for their appearance, such as tinea favosa (favus, or honeycomb-like due to *T. schoenleinii*) or tinea imbricata ("composed of overlapping parts"; ringworm due to *T. concentricum*).

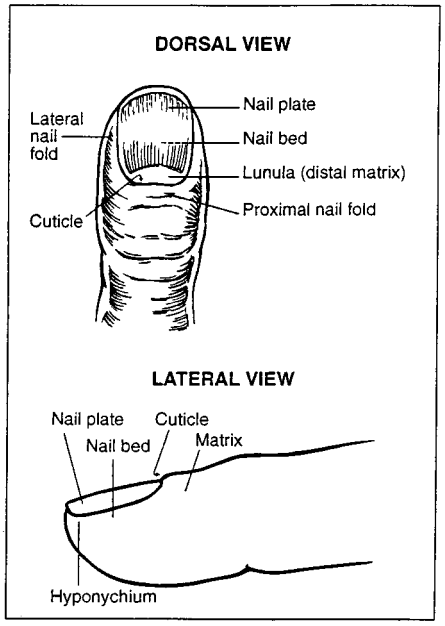

FIG. 1. The nail unit. Reprinted from reference 11 with permission of the publisher.

ANATOMY OF THE NAIL

A review of the anatomy of the nail unit and the process of nail growth may be helpful in understanding the pathogenesis of dermatophytic fungi in the nail unit. A diagram of the nail unit is presented in Figure 1 (11). It consists of the following structures: proximal and lateral folds, cuticle, matrix, nail plate (commonly called the nail), nail bed, and hyponychium. The cuticle is the horny layer of the proximal nail fold; it consists of modified stratum corneum and protects the nail matrix from infection (12). The nail matrix is the growth center of the nail. As the nail grows, cells of the nail matrix divide, differentiate, and keratinize and are incorporated into the nail plate. The distal, visible part of the matrix looks like a "half moon" and is called the lunula. The matrix extends approximately 5 mm proximally beneath the proximal nail fold (12). The nail plate is the largest structure of the nail unit and grows by sliding forward over the nail bed, whereupon the distal end becomes free of the nail bed (44). The hyponychium, the most distal component in the nail bed, is composed of epidermis that includes a granular layer similar to that seen in plantar and volar surfaces (12). Fingernails grow at a rate of 2 to 3 mm per month, and toenails grow at a rate of 1 mm per month. Therefore, it takes about 6 months to replace a fingernail and between 12 and 18 months to replace a toenail (12). This rate of growth is often decreased in the presence of peripheral vascular disease and onychomycosis and in the elderly (12).

CLASSIFICATION OF ONYCHOMYCOSIS

Four types of onychomycosis, characterized according to clinical presentation and the route of invasion, are recognized.

Distal Subungual Onychomycosis

Distal subungual onychomycosis (DSO) is the most common form of onychomycosis. It is characterized by invasion of the nail bed and underside of the nail plate beginning at the hyponychium (Fig. 2). The infecting organism migrates proxi-

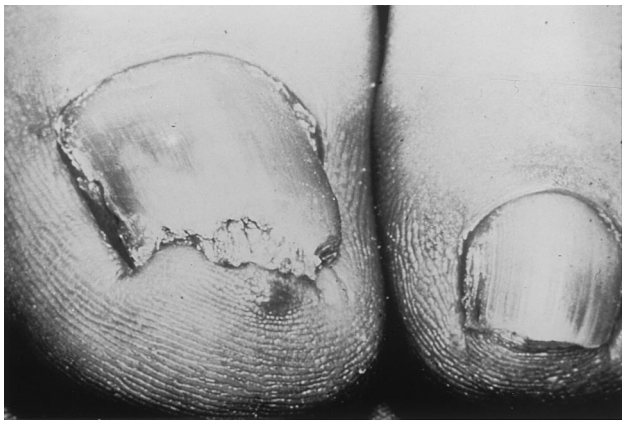

FIG. 2. Distal subungual onychomycosis. Courtesy of Gary Palmer.

mally through the underlying nail matrix. Mild inflammation develops, resulting in focal parakeratosis and subungual hyperkeratosis, with two consequences: onycholysis (detachment of the nail plate from the nail bed) and thickening of the subungual region. This subungual space then can serve as a reservoir for superinfecting bacteria and molds, giving the nail plate a yellowish brown appearance (12).

DSO is usually caused by the dermatophyte *T. rubrum* (26, 59), although *T. mentagrophytes*, *T. tonsurans*, and *E. floccosum* also are known to be causative. DSO may develop on the fingernails, toenails, or both, with infection of the toenails being much more common than infection of the fingernails; in the Finnish study (40), only 2 of the 91 patients with dermatophyte-related onychomycosis of the toenails also had fingernail involvement. Toenail infections were approximately 20 times more common than fingernail infections in the Ohio cohort (27). The increased frequency of toenail in comparison to fingernail infections probably reflects the greater incidence of tinea pedis than of tinea manuum.

Proximal Subungual Onychomycosis

Proximal subungual onychomycosis (PSO) is also known as proximal white subungual onychomycosis (PWSO), a relatively uncommon subtype, and occurs when organisms invade the nail unit via the proximal nail fold through the cuticle area, penetrate the newly formed nail plate, and migrate distally (Fig. 3). The clinical presentation includes subungual hyperkeratosis, proximal onycholysis, leukonychia, and destruction of the proximal nail plate. In the United States *T. rubrum* is the principal causative agent of PSO.

The pattern of growth in PSO is from the proximal nail fold on the lunula area distally to involve all layers of the nail (20). Although PSO is the most infrequently occurring form of onychomycosis in the general population, it is common in AIDS patients and is considered an early clinical marker of HIV infection (2). In one study of 62 patients with AIDS or AIDS-related complex and onychomycosis, 54 patients (88.7%) had PSO, with *T. rubrum* being the etiologic agent in more than half of these patients (20). In 54 patients, the feet were affected, and in 5 patients, the hands were infected; infections of both toenails and fingernails were present in 3 patients (20). Infection may also occasionally arise secondary to trauma.

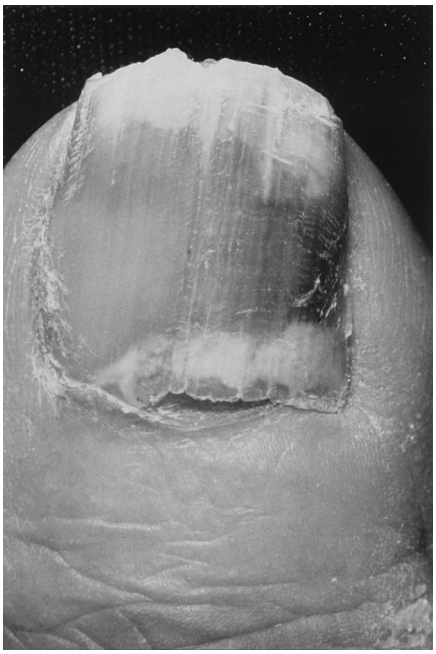

FIG. 3. Proximal subungual onychomycosis in a patient with AIDS. Courtesy of Gary Palmer.

White Superficial Onychomycosis

White superficial onychomycosis (WSO) is less common than DSO (estimated proportion of onychomycosis cases, 10%) (66) and occurs when certain fungi invade the superficial layers of the nail plate directly (Fig. 4). (Later, the infection may move through the nail plate to infect the cornified layer of the nail bed and hyponychium.) It can be recognized by the presence of well-delineated opaque "white islands" on the external nail plate, which coalesce and spread as the disease progresses. At this point, the nail becomes rough, soft, and crumbly (12). Inflammation is usually minimal in patients with WSO, because viable tissue is not involved (12). WSO occurs primarily in the toenails (66).

The most common etiologic agent in WSO is *T. mentagrophytes* (12). In addition, several nondermatophyte molds, including *Aspergillus terreus*, *Acremonium roseogrisum* (later confirmed to be *Acremonium potronii*), and *Fusarium oxysporum*, have been implicated by Zaias et al. (66).

FIG. 4. White superficial onychomycosis.

Candida Infections of the Nail

Candida nail infections occur in patients with chronic mucocutaneous candidiasis, and are caused by *C. albicans* (3). The organism invades the entire nail plate. *Candida* spp. may cause other syndromes, including onycholysis and paronychia. These forms occur more commonly in women than in men (3) and often affect the middle finger, which may come into contact with *Candida* organisms that reside in the intestine or vagina (66). *Candida* onychomycosis can therefore be divided into three general categories. (i) Infection beginning as a paronychia (infection of the structures surrounding the nail; also called a "whitlow"), the most common type of *Candida* onychomycosis (54), first appears as an edematous, reddened pad surrounding the nail plate. Invasion by *Candida* spp., unlike dermatophytic invasion, penetrates the nail plate only secondarily after it has attacked the soft tissue around the nail (12). After infection of the nail matrix occurs, transverse depressions (Beau's lines) may appear in the nail plate, which becomes convex, irregular, and rough and, ultimately, dystrophic (3, 12).

(ii) Patients with chronic mucocutaneous candidiasis are at risk for the second type of *Candida* onychomycosis, called *Candida* granuloma, which accounts for fewer than 1% of onychomycosis cases (12, 54, 66). This condition is seen in immunocompromised patients and involves direct invasion of the nail plate (30). The organism invades the nail plate directly and may affect the entire thickness of the nail, resulting, in advanced cases, in swelling of the proximal and lateral nail folds until the digit develops a pseudo-clubbing or "chicken drumstick" appearance (54).

(iii) Finally, *Candida* onycholysis can occur when the nail plate has separated from the nail bed. This form is more common on the hands than the feet (3). Distal subungual hyperkeratosis can be seen as a yellowish gray mass lifts off the nail plate. The lesion resembles that seen in patients with DSO (3).

Total Dystrophic Onychomycosis

Total dystrophic onychomycosis is used to describe end-stage nail disease, although some clinicians consider it a distinct subtype. It may be the end result of any of the four main patterns of onychomycosis. The entire nail unit becomes thick and dystrophic (65).

DIAGNOSIS OF ONYCHOMYCOSIS

The clinical presentation of dystrophic nails should alert the clinician to the possibility of onychomycosis; however, because fungi cause only about half of all nail dystrophies (30), the use of appropriate diagnostic techniques including direct microscopy and fungal culture is important to ensure correct diagnosis and treatment. The clinical appearance of the nail and the patient's history will help differentiate fungal from nonfungal etiologies of nail dystrophies. For example, predisposing factors for onychomycosis include diabetes mellitus, older age, hyperhidrosis, onychogryphosis, nail trauma, poor peripheral circulation, and immunosuppression (12). In the presence of subungual hyperkeratosis, yellow-brown discoloration, and onycholysis, onychomycosis is likely to be present. If the patient has a history of tinea pedis, particularly moccasin type, the case for this diagnosis is even stronger (12).

FIG. 5. Psoriasis affecting the nail. Courtesy of C. R. Daniel III.

Differential Diagnosis

Care should be taken to correctly identify signs and symptoms of other diseases that clinically mimic onychomycosis. These include psoriasis (the most common such disorder), lichen planus, bacterial infections, contact dermatitis, traumatic onychodystrophies, pachyonychia congenita, nail bed tumors, yellow-nail syndrome (rare), and idiopathic onycholysis. When psoriasis affects the nails, it is usually also present at other skin sites; however, in some cases nail involvement is the only sign (6). When psoriasis affects the nails, it can produce onycholysis resembling that associated with DSO (Fig. 5). A diagnosis of psoriasis is supported by the presence of fine pitting on the nail surface, the small salmon-colored "oil drop" sign of onycholysis that is not seen in onychomycosis, and fingernail involvement of both hands (28).

Approximately 10% of patients with lichen planus have abnormal nails. "Twenty-nail" dystrophy is a condition of unknown cause. Onychorrhexis (exaggerated longitudinal ridging) and "angel wing deformity," in which the central portion of the nail is raised and the lateral portion is depressed (28), are manifestations of lichen planus. A patient with 20 dystrophic nails is unlikely to have onychomycosis. Contact dermatitis occasionally resembles onychomycosis. The correct diagnosis is facilitated by knowledge of known contactants and the presence of contact dermatitis elsewhere on the body.

Finally, repeated nail trauma can cause distal onycholysis, leading to colonization of the affected space by microorganisms that produce pigmentation of the area. If the onycholytic nail is clipped to allow examination of the nail bed, the latter will be normal if the symptoms are caused by trauma rather than onychomycosis. Nail products containing formaldehyde may also cause onycholysis. In this situation, the nails may become yellow and all exposed nails are affected. A habit tic, often manifesting as a median furrow or depression in the middle of the nail, developed from picking at the nail cuticle, may also cause abnormalities of the nail.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.