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Tinea pedis: The etiology and global epidemiology of a common fungal infection

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Abstract

Tinea pedis, which is a dermatophytic infection of the feet, can involve the interdigital web spaces or the sides of the feet and may be a chronic or recurring condition. The most common etiological agents are anthropophiles, including *Trichophyton rubrum* sensu stricto, which is the most common, followed by *Trichophyton interdigitale* and *Epidermophyton floccosum*. There has been a change in this research arena, necessitating a re-evaluation of our knowledge on the topic from a multidisciplinary perspective. Thus, this review aimed to provide a solid overview of the current status and changing patterns of tinea pedis. The second half of the twentieth century witnessed a global increase in tinea pedis and a clonal spread of one major etiologic agent, *T. rubrum*. This phenomenon is likely due to increases in urbanization and the use of sports and fitness facilities, the growing prevalence of obesity and the aging population. For optimal patient care and management, the diagnosis of tinea pedis should be verified by microbiological analysis. In this review, we discuss the epidemiology, clinical forms, complications and mycological characteristics of tinea pedis and we highlight the pathogenesis, prevention and control parameters of this infection.

Introduction

Dermatophytosis, which is a fungal infection common worldwide, occurs in all age and sex groups and more than 70% of the population will experience this infection during their lifetime (Brooks & Bender, 1996). Over $500,000,000 per year is spent globally on medications that target dermatophytosis (Kane et al., 1997). Tinea pedis, an infection of the feet and toes, is the most common form of dermatomycosis in the post-pubescent period; this condition is a public health problem because of its contagious and recurrent nature (Merlin et al., 1999). Rippon (1988) revealed that 70% of the population is infected with athlete’s foot or tinea pedis, at some point in their life. Although tinea pedis has afflicted humanity for centuries, it was first described by Pellizzari in 1888 (Pellizzari, 1888). Djëlaleddin-Moukhtar (1892), a famous Ottoman Empire dermatologist in Paris, studied the dermatomycotic infection known today as “tinea pedis et manuum” or “Celal Muhtar” disease. Terming the infection “trichophytosis”, Djëlaleddin-Moukhtar (1892) described its etiology, differential diagnosis, prognosis and therapy. Subsequently, Whitfield (1908) and also Sabouraud believed tinea pedis to be a rare infection caused by the same organism that produced tinea capitis; however, the former frequently remained undiagnosed and was often treated inadequately (Merlin et al., 1999).

The reliable diagnosis and efficient treatment of tinea pedis is important. First, tinea pedis mimics many dermatologic diseases of the foot (Brod et al., 2007; Lin et al., 2011). Second, tinea pedis is also an important reservoir for dermatophytosis in other parts of the body. This infection is often transmitted by autoinoculation, which causes the additional conditions of tinea manuum, tinea inguinalis and tinea unguium (Daniel et al., 1997; Daniel & Jellinck, 2006; Daniel & Lawson, 1987). Third, when inappropriate treatment is received, it can lead to secondary bacterial infections and various allergic diseases (Al-Hasan et al., 2004; Woodfolk, 2005). Last, tinea pedis is the most common entry point for bacteria in cellulitis of the leg (Baddour & Bisno, 1985; Semel & Goldin, 1996) and is the most common cause of id reactions (Ilkit et al., 2012a). In this review, we aimed to provide a broad update of the epidemiology, pathogenic mechanisms, clinical forms and complications of tinea pedis. In addition, we provide a comprehensive overview of accurate and reliable diagnostic and management protocols as well as prevention and control strategies for allergists, clinical microbiologists, dermatologists, family physicians, general practitioners, infectious disease clinicians, public health workers and sports medicine specialists.
Methods

We searched PubMed/MEDLINE and Google Scholar for critical reviews on dermatophytes from July 2000 to July 2013 using the following search terms: ‘tinea pedis’, ‘‘athlete’s foot’’, and ‘‘foot diseases’’. We then reviewed the retrieved reports to determine whether they should be included in the present study. We excluded papers that focused on other foot diseases, such as erythrasma, contact dermatitis or pemphigus. The scope of this review is therefore limited to tinea pedis studies and not all foot diseases are discussed herein.

Taxonomy: current state

Dermatophytes are aligned with the family Arthrodermataceae, a monophyletic group of filamentous fungi that are closely related to the dimorphic fungi in the order Onygenales (most closely related to the genus Coccidioides) and the class Eurotiomycetes. Three anamorphic (asexual or imperfect) dermatophyte genera (Trichophyton, Microsporum and Epidermophyton) have been described (Padhye & Summerbell, 2005; Weitzman & Summerbell, 1995); however, the dermatophytes that are also capable of reproducing sexually (i.e., able to produce ascosoma with asci and ascospores) are classified in the teleomorphic genus Arthroderma (Weitzman et al., 1986). Remarkably, all sexual and asexual dermatophytes are closely related and are members of Arthrodermataceae (Padhye & Summerbell, 2005). Depending on their host preferences and natural habitats, dermatophytes are also divided into three ecological groups: anthropophiles, zoophiles and geophiles (Padhye & Summerbell, 2005; Summerbell et al., 2007; Weitzman & Summerbell, 1995).

The post-1999 modern systematics of dermatophytes extensively improved and simplified our knowledge of any given species in question and greatly increased our understanding of population genetics (Abdel-Rahman, 2008; Gra¨ser et al., 1999a, 2008; Heidemann et al., 2010; Trotha et al., 2003). Differentiation between the zoophilic strains of T. interdigitale and T. mentagrophytes is not possible using conventional methods (Heidemann et al., 2010).

Emergence of T. rubrum and the T. mentagrophytes complex

Anthropophilic dermatophytes are primarily associated with humans and rarely infect other animals (Weitzman & Summerbell, 1995). The changing incidence of dermatophyte colonization and their associated dermatophytes, as well as their potential for spreading throughout the population, became evident after the two world wars (Rippon, 1985). The change in the dermatophyte spectrum over the last century has been extensively reviewed (Philpot, 1977; Rippon, 1985; Seebacher et al., 2008). Although the anthropophiles T. rubrum, T. interdigitale and E. floccosum are the major agents of tinea pedis, zoophiles and geophiles have also been recovered from foot lesions, albeit less frequently (Borman et al., 2007; Summerbell et al., 2007).

By the late 1960s, the anthropophilic species that cause tinea pedis (T. rubrum and T. interdigitale) were solidly established and tinea capitis had become a relatively rare infection (Aly, 1994; Philpot, 1977; Rippon, 1985; Seebacher et al., 2008). In addition, anthropophilic T. interdigitale has been progressively replaced by T. rubrum as the primary etiologic agent of tinea pedis and tinea unguium (Seebacher et al., 2008). For example, in the British Isles, these two common causes of foot infection comprised 80% of all dermatophytes isolated in 1980 and 90% of the isolates in 2005 (Borman et al., 2007). This trend is also typical in central and northern Europe and is linked to the increased incidence of tinea pedis (Seebacher et al., 2008). In Germany, T. rubrum increased from 41.7% of all dermatophyte isolates in 1950 (Götz, 1952) to 82.7% in 1993 (Tietz et al., 1995). Although the exact reasons for the predominance of these two organisms remain unclear, their increased prevalence and continued dominance may be related to genuine changes in lifestyle, including increased urbanization and ready access to communal sports facilities (Borman et al., 2007). Seebacher et al. (2008) suggested that the predominance of T. rubrum could be explained by the wide distribution of tinea pedis and tinea unguium. Conversely, the relative prevalence of E. floccosum decreased 11-fold from 1980 (7.31%) to 2000 (0.63%) in the UK (Borman et al., 2007). However, a different spectrum of dermatophytes was reported in an Iranian study in which E. floccosum was the predominant dermatophyte species (31.4%) over a three-year period (1999–2001) (Falahati et al., 2003).
Sex in dermatophytes

Many fungi have the ability to reproduce both sexually and asexually (Coppin et al., 1997). Fungi have been hypothesized to preferentially clonally expand through asexual reproduction in stable environmental niches; however, they may also undergo genetic exchange via sexual reproduction in response to stressful conditions, such as new environments or changes in the human host, including the use of antimicrobial therapy (Coppin et al., 1997; Nielsen & Heitman, 2007).

Sexual reproduction has also been reported in a large number of dermatophytes, predominantly in geophilic species, although the genomic basis of the mating type has not been studied (White et al., 2008). Li et al. (2010) frequently observed sexual reproduction in one geophilic dermatophyte (M. gypseum) but did not often observe it in zoophilic (M. canis and T. equinum) or anthropophilic (T. rubrum and T. tonsurans) dermatophytes. Sexual reproduction is particularly rare in anthropophilic dermatophytes. However, the identification of mating type (MAT) loci in five dermatophyte species has indicated that most anthropophilic dermatophytes retain a MAT locus and extant sexual or parasexual cycles.

Molecular typing strategies

With the introduction of molecular methods such as the sequencing of the internal transcribed spacer (ITS) region for the differentiation of dermatophytes, it has become clear that the phenotypes and genotypes of this group of fungi are not always congruent (Gräser et al., 1999a, 2000a,b). According to genetic and phylogenetic studies, dermatophytes are a homogeneous group with recent evolutionary divergence, despite their diverse morphological and host characteristics (Gräser et al., 2006, 2008; Kanbe, 2008).

Ohst et al. (2004) identified two strains from among 124 isolates of T. rubrum using a single microsatellite marker (T1). Gräser et al. (2007) described 55 unique genotypic combinations in 233 isolates of T. rubrum and three multilocus genotypes in T. violaceum using seven microsatellite markers, including the T1 marker. In one study, T. rubrum tinea pedis isolates were inoculated onto a single plate and two to five colonies per plate were typed using a PCR-based analysis of repeats in the rRNA intergenic spacer. Interestingly, each patient was colonized by only a single isolate (Rad et al., 2005). Using PCR fingerprinting, 19 profiles were observed among 42 isolates of T. mentagrophytes var. interdigitale (Jackson et al., 2006). Several studies have attempted to address numerous relevant clinical and epidemiological questions concerning dermatophytes (Gräser et al., 1999b, 2007; Guoling et al., 2006; Gupta et al., 2001; Jackson et al., 2006; Ohst et al., 2004; Rad et al., 2005). In general, molecular typing strategies are used to explore the population structure and regional distribution of dermatophyte strains, such as T. rubrum (Abdel-Rahman, 2008).

The T. rubrum complex

Anthropophilic T. rubrum (Castellani) Semon 1910, which is the most prevalent species of this complex, was first discovered and described as Epidermophyton rubrum (Castellani, 1910), after the other primary dermatophytes had already been recognized for several decades. T. rubrum typically causes chronic infections and may have a tendency to spread to other anatomical sites (Zaias & Rebell, 2003). This species was suggested to have evolved in the late 19th century as a cause of chronic tinea corporis from the endemic areas of Southeast Asia. T. rubrum has since spread throughout the world as the predominant etiological agent of tinea pedis and tinea unguium (Rippon, 1988). Its prevalence is related to increases in traveling, sporting events, the use of occlusive footwear and the use of public facilities, such as communal showers and swimming pools (Havlickova et al., 2008; Lacroix et al., 2002; Seebacher et al., 2008; Weitzman & Summerbell, 1995). Most notably, T. rubrum can survive (without propagation) up to 18 months in its arthroconidial form (Baer et al., 1955), which may be responsible for its clonal spread. However, as noted by Rippon (1988), the arthroconidia (hyphal fragments) of T. rubrum do not survive as long as those of other species (e.g., E. floccosum).

For many years, no studies have identified any related teleomorphic species suggestive of clonal reproduction associated with the T. rubrum complex (Gräser et al., 2007). In one study, Gräser et al. (1999b) analyzed 57 DNA loci representing 12 markers of 96 T. rubrum strains and remarkably, none of the methods revealed DNA polymorphisms, indicating a strictly clonal mode of reproduction and a strong adaptation to human skin. This high degree of morphological diversity contrasts with the homogeneity of the genome, as revealed by anonymous DNA markers. T. rubrum strains were later distinguished by polymorphisms in the number of subrepeat elements in the ribosomal nontranscribed spacer region (Gupta et al., 2001; Jackson et al., 2000; Rad et al., 2005). In addition, T. rubrum showed a wide variety of phenotypic features, including the presence or absence of reflexively branching hyphae, micro- and macro-arthroconidia, red colony pigmentation and urease activity, whereas its genotype was reported to be stable (Guoling et al., 2006). Subsequently, Gräser et al. (2007) verified this lack of correlation between the multilocus genotypes and any of the phenotypical characteristics. Within the T. rubrum complex, although the urease-positive and granular T. rauitischeckii are more strongly associated with tinea corporis, cases of tinea pedis have already been described (Kane, 1990). T. megninii is almost exclusively confined to Portugal, Corsica and Sardinia and has been recovered from a well-defined foot lesion in a patient in Canada (Kane & Fischer, 1975). Recently, the genome sequencing of T. rubrum and four related species (T. equinum, T. tonsurans, M. canis and M. gypseum) was described by Martinez et al. (2012).

The T. mentagrophytes complex

T. mentagrophytes (Robin) Blanchard 1853 was first described in the follicles of a man’s beard (Robin, 1853). This isolate likely corresponded to the granular type of the species belonging to A. simii (Gräser et al., 1999a). Subsequently, the T. mentagrophytes complex was shown to be heterogeneous, containing several species and varieties that broadly differ in their ecology and have a wide range of hosts, including humans and animals (Beguin et al., 2012; Georg, 1954; Gräser et al., 1999a; Heidemann et al., 2010;
Members of *T. mentagrophytes sensu lato* frequently cause more inflammatory types of infections compared with *T. rubrum*, which typically causes chronic infections (Zaías & Rebell, 2003). The downy-type (cottony and velvety) and granular-type isolates of *T. mentagrophytes sensu lato* differ in their clinical, epidemiological and virulence properties (Georg, 1954; Ota, 1933). The downy-type isolates were primarily isolated from chronic, low-grade infections and were more commonly involved in tinea pedis in city dwellers, whereas the granular-type infections were more acute and suppurative and were generally observed in rural settings (Georg, 1954).

A decade ago, a deep absceding case of tinea barbae, caused by a zoophilic strain of *T. interdigitale*, was also reported (Trotha et al., 2003). Consistent with these findings, Sun et al. (2010) reported that the downy-type isolates from human tinea pedis and onychomycosis shared the same sequence as type CBS 428.63, the anthropophilic strain of *T. interdigitale*, whereas the granular-type isolates of tinea faciei, tinea capitis and tinea corporis were compatible with the zoophilic strain of *T. interdigitale* (CBS 318.56). The authors recovered *T. erinacei* from only two human cases, one with tinea faciei and the other with tinea manuum, which were compatible with *T. erinacei* CBS 511.73.

### Epidemiology

Several researchers have used different study sizes, designs and target groups to examine the epidemiological characteristics of tinea pedis and have found that its incidence is not associated with a specific racial or ethnic group (Götz & Hantschke, 1965; Ilkit et al., 2005; Lacroix et al., 2002; Noguchi et al., 1995; Perea et al., 2000; Triviño-Duran et al., 2005). The prevalence of tinea pedis increases with age and it is more frequent in adults aged 31–60 years, followed by adults aged >60 years (Drakensjö & Chyrssanthou, 2011; Szepietowski et al., 2006); it is rare in children (Andrews & Burns, 2008). The risk of tinea pedis has been shown to be higher in men than in women (Drakensjö & Chyrssanthou, 2011) and it is more common in developed countries. It is clear that certain occupational groups are exposed to a particularly high risk of infection. For example, up to 72.9% of miners (Götz & Hantschke, 1965), 58% of soldiers (Noguchi et al., 1995) and 31% of marathon runners (Lacroix et al., 2002) examined had mycologically proven tinea pedis. The prevalence of tinea pedis was 29.5% in mosque attendees (Ilkit et al., 2005). The exposure of these specific populations to sweating, trauma, occlusive footwear and communal areas predisposes these groups to an increased incidence of tinea pedis (Field & Adams, 2008). In an elegant study, Szepietowski et al. (2006) reported that tinea pedis was the most common concomitant dermatomycosis, found in 33.8% of all of patients with toenail onychomycosis. The authors noted that the interdigital subtype was the most common form of tinea pedis and was present in 65.4% of participants. In one study, the prevalence of palmoplantar keratoderma in Sézary syndrome was reported to be 61.6% and co-existing tinea pedis was present in 52.9% of participants (Martin & Duvic, 2012).

In a Spanish study, the prevalence of tinea pedis was reported to be low (2.9%) in the general adult population; however, participation in sports and the use of common showers increased the risk of tinea pedis ($p < 0.05$) but not the presence of concomitant diseases (e.g., diabetes mellitus, psoriasis or vascular diseases) ($p > 0.05$) (Perea et al., 2000). In line with this finding, a 40% prevalence of tinea pedis has been reported in patients with pedal interdigital macerations, although no meaningful difference was observed when diabetic and non-diabetic participants were compared ($p > 0.05$) (Legge et al., 2008). In addition, dermatophytes which are strongly associated with the presence of tinea pedis, have been isolated from normal-appearing toenails (Walling, 2009). Children are exposed to three primary sources of infection: (i) families, (ii) schools and (iii) swimming pools. In a previous study, tinea pedis was reported to have prevalence rates of 6.6% and 1.6% in 11–14-year-old boys and girls, respectively and 2.2% in 7–10-year-old boys (English & Gibson, 1959). One study demonstrated that tinea pedis (2.8%) had a higher prevalence than tinea capitis (0.23%) in 3–15-year-old children (Triviño-Duran et al., 2005).

### Pathogenesis

Dermatophyte infections are caused by arthrospores or asexually reproducing conidia. High temperatures, an alkaline pH and hyperhidrosis facilitate pedal infections by these organisms. Host factors that can enhance these infections include broken skin, maceration of the skin and immunosuppression. However, *Pseudomonas aeruginosa*, transferrin, natural killer cells and CD14-positive monocytes inhibit fungal invasion (Brasch, 2009). The most common dermatophyte infections are due to the absence of sebum, which is a natural inhibitory secretion; sebum is not present in the plantar region due to the absence of sebaceous glands.

Dermatophytes release various enzymes (e.g. keratinases, metalloproteases, cysteine dioxygenase and serine proteases), produce lipases and ceramides and invade the superficial keratin (Grumbt et al., 2013; Mendez-Tovar, 2010). Keratinocytes not only constitute a physical barrier against dermatophytes but also play a role in cutaneous immune reactions (Tani et al., 2007). They express pattern recognition receptors, such as Toll-like receptors (TLRs) and dectin-1, which promote the release of various proinflammatory cytokines and chemotactic factors and cause inflammatory reactions, such as redness and swelling (Brasch, 2010). Keratinocytes also release antimicrobial peptides, including defensins, cathelicidins and psoriasin, which prevent fungal invasion (Brasch, 2009; López-García et al., 2006). The release of beta-defensins is decreased in patients with atopic dermatitis, which leads to frequent dermatophyte infections. Dermatophyte infections are considered to be rare in psoriatic patients; these individuals have no greater prevalence of tinea pedis and tinea unguium compared to control patients ($p > 0.05$) (Hamnerius et al., 2004).

Chemotactic factors recruit neutrophils and monocytes (macrophages), which are inflammatory phagocytes that engulf dermatophytes and release cytokines (Almeida, 2008). They also produce reactive oxygen species (ROS), such as superoxide, hydrogen peroxides and hydroxyl...
radicals, that result in damaged proteins, lipids and DNA, thereby destroying the phagocytosed pathogens (Ozturk et al., 2013). However, the cell wall mannans of \textit{T. rubrum} decrease the lymphoproliferative response (Mendez-Tovar, 2010). Local fungal infections induce the production of circulating antibodies and activate T-lymphocytes, leading to various localized or generalized inflammatory reactions called "id reactions" (Ilkit et al., 2012a). The pathogenesis of tinea pedis is illustrated in Figure 1 (Brasch, 2010; Fritz et al., 2012; Grumbt et al., 2013; Martinez et al., 2012; Tani et al., 2007; Woodfolk, 2005).

**Clinical forms**

The importance of tinea pedis is two-fold: first, tinea pedis is a common infection that is becoming more widespread over time and second, the foot is a pedal fungal reservoir from which fungi can spread elsewhere (Daniel & Jellinck, 2006; Daniel & Lawson, 1987). Approximately one-third of patients with tinea pedis have a concomitant nail infection (Szepietowski et al., 2006). However, asymptomatic infections (occult tinea pedis) are common, with a prevalence of 36-88%, particularly among athletes. \textit{Trichophyton interdigitale} causes the majority of occult cases of tinea pedis (Atteye et al., 1990; Auger et al., 1993; Kamihama et al., 1997) and damp foot conditions may lead to aggravated symptoms due to mixed infections with bacteria (Auger et al., 1993). Patients are often unaware of tinea pedis and tinea unguium and treatments are sometimes insufficient (Watanabe et al., 2010). Tinea pedis typically presents in four different forms: (i) interdigital, (ii) inflammatory (vesicular), (iii) chronic hyperkeratotic (moccasin) and (iv) ulcerative.

**Interdigital tinea pedis**

The most common form is interdigital tinea pedis, which is predominantly caused by \textit{T. rubrum} followed by anthropophilic \textit{T. interdigitale} (Havlíčková et al., 2008). A more common role of anthropophilic \textit{T. interdigitale} among the members of \textit{T. mentagrophytes sensu lato} has been reported in many parts of the world, such as Europe (Beguin et al., 2012; Heidemann et al., 2010) and East Asia (Sun et al., 2010). In contrast, \textit{T. mentagrophytes sensu stricto} is very rare in western Europe, at least and no association has been reported with common pets such as guinea pigs, dogs or cats.
The primary risk factors for the development of tinea pedis include hot humid climates, sporting activities and hyperhidrosis (Caputo et al., 2001). Clinically, interdigital tinea pedis is characterized by interdigital erythema, scaling, maceration and fissuring (Figure 2A). Lesions are typically observed between the fourth and fifth toes and are collectively called dermatophytosis simplex. The most common reasons for clinical admission are itching, burning and malodor. The dorsal surface of the foot is generally unaffected, but adjacent plantar areas may be involved. If tinea pedis is mistakenly treated with topical corticosteroids, the corticosteroids suppress the host immune response, resulting in reduced inflammation and pruritus. However, this immunosuppressive state leads to the spread of the fungal infection (tinea incognito) (Glick & Khachemoune, 2012) (Figure 2B). Extensive spreading to the dorsum of the feet may be observed in patients with human immunodeficiency virus (HIV) and in patients with T-cell function disorders. Tinea pedis may also become resistant to antifungal therapy in these immunosuppressed patients (Al-Hasan et al., 2004).

Corynebacterium minutissimum, Gram-negative bacteria and Candida species can cause interdigital erythema, scaling and maceration, which should therefore be considered in the differential diagnosis (Lin et al., 2011). Interaction with bacteria is also possible in the toe cleft spaces, with a clinically more severe bacterial infection having a polymicrobial etiology (complex infection) (Leyden,
while walking (Grigoriu et al., 1987). One or both feet may be involved and the frequency of toenail infections increases with the duration of the disease (Figure 2E). Approximately 50% of these patients have (only) one palm involved, which leads to the “two feet-one hand” syndrome (Figure 2F). Several nails of the involved hand may also be infected. The clinical features of tinea manuum are similar to those of moccasin tinea pedis; this syndrome is common, but the cause of the unilateral involvement of the hands is unknown. In a study of 80 patients with this syndrome (90% men and 10% women), tinea was found to begin in the feet (Daniel et al., 1997). One molecular study, which included 113 cases of “two feet-one hand” syndrome, showed that 94.5% of paired isolates from the feet and the hand were composed of the same species and that 80% of these pairs had the same genotypes. This syndrome can be found in patients with lowered immunocompetence, such as diabetics and the condition is frequently associated with T. rubrum (Zhan et al., 2010). Tinea manuum most likely develops as a result of scratching the foot (Daniel et al., 1997).

**Ulcerative tinea pedis**

Ulcerative tinea pedis, which is typically caused by anthropophilic T. interdigitale, is characterized by spreading vesiculopustular lesions, ulcers and erosions and is often accompanied by a secondary bacterial infection. The lesions are usually macerated and have scaling borders. This infection typically begins in the third and fourth interdigital spaces and extends to the lateral dorsum and the plantar surface and occasionally, large areas, even the entire sole, can be sloughed. This type of tinea pedis is commonly observed in immunocompromised and diabetic patients (Legge et al., 2008). The most common complications are cellulitis, lymphangitis, fever and malaise (Grigoriu et al., 1987).

In addition to these common forms, verrucous and pustular forms have also been reported (Figure 3A and B). Qiangqiang et al. (2001) reported the case of an 8-year-old boy with verrucous tinea pedis caused by E. floccosum. The lesions initially occurred on his right heel but spread to involve the lower extremities. He was treated with oral ketoconazole for four months. In another study, Hirschmann & Raugi (2000) reported a 78-year-old man with pustular tinea pedis due to T. rubrum. Bacterial cultures of his pustular lesions were sterile and these lesions subsequently resolved within six weeks of griseofulvin treatment.

**Complications of tinea pedis**

Tinea pedis can lead to several complications, including id reactions, bacterial superinfection, Majocchi’s granulomas, tinea incognito, lymphangitis and cellulitis and can spread to the nails, other skin areas and scalp (Figure 4A and B) (Degreef, 2008).

**Cellulitis**

The most common entry point for bacteria in cellulitis of the lower extremities is tinea pedis, particularly the interdigital type (Figure 4C). Two case-control studies have demonstrated a significantly higher rate of tinea pedis in patients with cellulitis (Baddour & Bisno, 1985; Semel & Goldin, 1996).
Figure 3. A verrucous plaque on the lateral side of the heel due to *T. rubrum* (A); dry, hyperkeratotic scale involving the entire plantar surface in a patient with chronic hyperkeratotic tinea pedis and verrucous plaque (arrow) due to verruca plantaris (B).

Figure 4. Complications from tinea pedis. Vesicles on the back of a foot from a patient infected with tinea pedis (A); an erythematous, scaly, crusted patch on the back of the foot due to tinea pedis, with onychomycosis presenting as subungual hyperkeratosis of the ‘‘hallux’’ (B); maceration between the toes from secondary tinea pedis in a patient with cellulitis presenting as erythema and edema of the leg and foot (C); and vesicles and crusts on the wrists due to interdigital tinea pedis (D).
Although dermatophytes do not cause cellulitis, they lead to scaling and fissuring, which impair the skin barrier and provide a suitable niche for bacterial entry (Björnsdóttir et al., 2005). Tinea pedis has also been associated with an increased incidence of cellulitis in patients with saphenous venectomy. In one study, 40 of 42 patients had tinea-pedis-associated cellulitis following saphenous venectomy; however, additional episodes were prevented by antifungal treatment (Hirschmann & Gaugi, 2012). These studies have shown that patients with lower-limb cellulitis should be examined for tinea pedis and, if positive, that antifungal treatments should be administered to prevent the development of recurrent episodes. Furthermore, underlying causes, such as diabetes mellitus, obesity and poor hygiene, should also be investigated (Al-Hasan et al., 2004; Bristow & Spruce, 2009). In several patients with dermatophytosis complex, the genera of *Pseudomonas*, *Proteus* and *Klebsiella* led to Gram-negative cellulitis. In these patients, demonstration of the fungal elements may be difficult because an excess of Gram-negative bacteria may inhibit fungal growth, making it more difficult to detect fungal pathogens upon potassium hydroxide (KOH) examination. For this reason, bacterial cultures of the skin may detect Gram-negative bacteria, but fungal cultures are typically negative. Treatment of these underlying fungal and Gram-negative bacterial infections can lead to faster improvement of the cellulitis (Day et al., 1996).

**Id reaction**

The id reaction is a type of secondary immunological reaction caused by a local inflammatory infection at a distant site (Figure 4D). Local infections activate circulating antibodies or activated T-lymphocytes, leading to various localized or generalized inflammatory reactions. Various fungal, bacterial, viral and parasitic infections can cause id reactions (Ilkit et al., 2012a); however, the most common cause is a superficial fungal infection, particularly tinea pedis. The incidence of dermatophytids due to tinea pedis has been reported to be 17%. Dermatophytids are often observed on the hands and sides of the fingers (Veien et al., 1994) and in some patients, the lesions are initially dominated by vesicles and bullae. Subsequently, papules or pustules appear at a secondary site, typically the fingers or palmar surfaces and the interdigital spaces (Brlyd et al., 2003; Kaaman & Torssander, 1983; Veien et al., 1994). Generalized follicular papules have rarely been reported (Iglesias et al., 1994).

**Majocchi’s granuloma**

Dermatophytes can invade the hair follicles and cause perifollicular granulomatous inflammation or Majocchi’s granuloma. Predisposing factors include the long-term use of potent topical corticosteroids or chemotherapeutic agents as well as systemic immunosuppression (Ilkit et al., 2012b). The papules and nodules can occur alone or on the more active borders of erythematous plaques. These lesions can also mimic Kaposi’s sarcoma (Brod et al., 2007).

**Asthma and atopic diseases**

Dermatophytic infections may induce a T-helper type 2 response (Th2) that can aggravate atopy; therefore, these infections may complicate allergies and asthma and may contribute to refractory atopic disease (Al-Hasan et al., 2004; Woodfolk, 2005). Ward et al. (1989) described “Trichophyton asthma” in 12 adult patients with chronic rhinitis and asthma, demonstrating an immediate hypersensitivity to *Trichophyton* spp. in 10 of the 12 patients. Mungan et al. (2001) showed that the rates of sensitivity to *T. rubrum* were higher in patients with intrinsic asthma than in the control groups and they suggested that these patients should be examined for signs of fungal infection and tested to determine their immediate hypersensitivity to dermatophyte antigens. Furthermore, superficial fungal infections can trigger atopic dermatitis and antifungal treatment improves these dermatitis symptoms (Klein et al., 1999).

**Laboratory methods**

In this review, we present a brief update on the practical data and experiences of several groups. To avoid misdiagnoses, the identification of dermatophytic infections requires both a fungal culture and the microscopic examination of skin scrapings or culture-independent molecular tools (Arabatzis et al., 2007; Bergmans et al., 2010; Verrier et al., 2013). The collection, transport, storage and handling of specimens; diagnostic techniques; and methods for the identification of dermatophytes are well described in several reviews (Robert & Pihet, 2008; Weitzman & Summerbell, 1995) and textbooks (Kane et al., 1997; Padhye & Summerbell, 2005; Rippon, 1988; Summerbell et al., 2007).

In clinical practice, tinea pedis is treated by dermatologists, family physicians and occasionally, general practitioners. With the exception of dermatologists, tinea pedis is routinely diagnosed without mycological information and its diagnosis is typically based on clinical findings. However, tinea pedis can mimic various vesiculobullous and scaly erythematous diseases, such as psoriasis, herpetic infections, cellulitis, contact dermatitis, erythrasma, impetigo, bacterial toe-web infections, candidiasis and pemphigus (Figure 5) (Lin et al., 2011; Sweeney et al., 2002). For this reason, a definitive diagnosis requires some degree of laboratory analysis (Noble et al., 1998). The diagnosis of tinea pedis is typically confirmed by direct microscopic examination with KOH preparations and by a fungal culture of skin scrapings; however, there are several disadvantages to these methods, including the false-positive result termed “mosaic fungus” (Padhye & Summerbell, 2005; Robert & Pihet, 2008; Weitzman & Summerbell, 1995). Histopathological examination with periodic acid-Schiff (PAS) staining has been successfully used (Noble et al., 1998) and the improved sensitivity of molecular tools makes dermatophyte identification possible when the fungus fails to grow in culture (Verrier et al., 2013).

KOH examination is the first screening tool used to identify fungal hyphae and spores. For an accurate microscopic diagnosis, the sampling method is important. The lesions should first be gently cleaned with a 70% alcohol swab to remove traces of skin products or medications. The skin scrapings should be made using a blunt scalpel (No. 15). If multiple lesions are present, the region selected for the
sampling is important because the active advancing border of
the lesion or the roof of the vesicle is preferred to old, loose
scales.

The obtained cellular material should be placed on a
microscopic slide and a 15–20% KOH solution should be
applied. After 15–30 minutes, the specimens can be examined
under a microscope. The presence of septated hyphae and
spores suggests the diagnosis of dermatophytic infections.
A positive result for fungal elements is sufficient tojustify
starting treatment because identification of the dermatophytic
species does not typically affect the choice of treatment.
The addition of Parker blue ink, chlorazol black and rapid contrast
stains may facilitate the identification of hyphae and spores
(Lim & Lim, 2008). Although calcofluor white yields fewer
false-negative results compared to KOH, it requires a
fluorescent microscope, which limits its use in clinical
practice in undeveloped or developing countries (Markus
et al., 2001). However, most of the larger microbiology
laboratories (at least in the USA, UK, France, Germany and
Japan) possess such equipment.

Importantly, in macerated or erosive-vesiculobullous
lesions, Gram-negative bacterial co-infections contribute to
diminished culture sensitivity (Field & Adams, 2008) or it may
difficult to detect fungal elements; therefore, negative
direct microscopic results do not exclude the possibility of
fungal infections. In these cases, a fungal culture is usually
used to detect the causative fungi (Noble et al., 1998).

Antifungal sulfur compounds secreted by some bacteria (such

Figure 5. Differential diagnosis of tinea pedis. Coral-pink color fluoresces under a Wood’s lamp examination (A); maceration between the toes due to
erythasma (B); plentiful “tadpole cells” without hyphae and bacteria in the Tzanck smear examination (C); a patient with contact dermatitis
mimicking vesicular tinea pedis (D); “dyskeratotic acantholytic cells” and cocci in the Tzanck smear test (E) in a patient with an erosive-
vesiculobullous lesion on the heel due to bullous impetigo (F); plentiful bacilli in a cytologic examination (G) of a maceration with green color between
the toes due to a toe-web infection with a *Pseudomonas* sp. (H); Tzanck smear examination revealing acantholytic cells (I) in a patient with vesicular
lesions of the feet due to pemphigus herpetiformis (J); Tzanck smear examination reveals acantholytic cells (K); maceration between the toes due to
Hailey-Hailey disease (L); cytology showing a multinucleated giant cell and acantholytic cells (M); a patient with zona zoster (herpes zoster)
mimicking vesicular tinea pedis (N); Tzanck smear test revealing intra- and extracellular *Leishmania* parasites (O); patient with cutaneous
leishmaniasis resembling infected tinea pedis (P); an erythematous plaque with pustules, vesicles and thickened scaly and brown crusts on the plantar
surface of the foot in a patient with palmoplantar pustulosis (Q); and peeling skin on the plantar surface of the foot in a patient with peeling skin
syndrome (R).
In vitro (i) the presence of neutrophils, (ii) compact orthokeratosis corneum can be associated with dermatophyte infections: be adopted in certain cases, it is not standard procedure in narrow the differential diagnosis; although histopathology can negative, a histopathological examination can be performed to activity (Ates et al., 2008).

Laboratory media (Döğen & Ilkit, 2013; Ilkit et al., 2012c), or using several specific media that minimize the carryover dermatophytes from each toe web by hand (Sano et al., 2005) culture does not always exclude tinea pedis. Rapidly culturing sensitive, whereas the latter is more specific. A negative fungal culture is used extensively in many laboratories for the routine diagnosis of tinea pedis (in combination with direct microscopic examination). In addition, many centers routinely culture all dermatology specimens as this provides invaluable epidemiological data concerning changes in dermatophyte prevalence and the species spectrum. Indeed, several studies have reported that only a small proportion of samples are microscopy negative and culture positive (Arabatzis et al., 2007; Borman et al., 2007; Levitt et al., 2010; Verrier et al., 2013). Fungal culture is also important in cases refractory to antifungal treatment. Although a fungal culture is inexpensive, it is time-consuming and can require 2-3 weeks to obtain positive results (Noble et al., 1998). Levitt et al. (2010) showed that the KOH smear and fungal culture are complementary diagnostic tools: the first test is very sensitive, whereas the latter is more specific. A negative culture does not always exclude tinea pedis. Rapidly culturing dermatophytes from each toe web by hand (Sano et al., 2005) or using several specific media that minimize the carryover effect of topical antifungal medications (Adachi & Watanabe, 2007; Nakashima et al., 2002) have improved the diagnosis of tinea pedis. Our group has also discussed the diagnostic value of conventional techniques, including physiological tests (Ates et al., 2008), improved conidia formation using several laboratory media (Döğen & Ilkit, 2013; Ilkit et al., 2012c), in vitro hair perforation tests (Gümrül et al., 2013) and urease activity (Ates et al., 2008).

When direct microscopic examination and culture are negative, a histopathological examination can be performed to narrow the differential diagnosis; although histopathology can be adopted in certain cases, it is not standard procedure in many microbiology laboratories. Three changes in the stratum corneum can be associated with dermatophyte infections: (i) the presence of neutrophils, (ii) compact orthokeratosis and (iii) the presence of the ‘‘sandwich sign.’’ The last sign is characterized by hyphae between the upper normal basket-weave stratum corneum and the lower layer of the parakeratotic stratum corneum. The detection of fungal elements is difficult when the histopathological examination is performed using hematoxylin and eosin (H&E) stain. In H&E-stained sections, hyphal elements are detected in only 57% of PAS-positive cases of tinea. Moreover, the number of fungi observed in the horny layer is typically low and thus may be easily overlooked, even when they are stained with PAS or GMS (Weedon, 2010). If these confirmatory stains are also negative, the histopathological findings may mimic dyshidrotic dermatitis (Guarner & Brandt, 2011). For this condition, tissue homogenate cultures and molecular-based techniques, such as PCR, may be used to detect dermatophytic fungi (Garg et al., 2009; Kanbe, 2008).

Nested PCR is not only rapid but also simple and inexpensive in comparison to other molecular methods for the detection of dermatophytes (Garg et al., 2009; Verrier et al., 2013). The fungal pathogen can be identified within 48 hours using a nested PCR/sequencing assay, whereas the results from a culture require at least 2 weeks (Verrier et al., 2013). Real-time PCR has also been successfully used to identify dermatophytic fungi from clinical samples and from cultures (Arabatzis et al., 2007; Bergmans et al., 2010), including rare macroconidia-producing dermatophyte species (Yüksel & Ilkit, 2012). Recently, a Matrix-Assisted Laser Desorption/ Ionization-Time-of-Flight Mass Spectroscopy (MALDI-TOF MS) procedure was also successfully used for the identification of clinical dermatophyte species (L’Ollivier et al., 2013).

Treatment

Tinea pedis can be treated with topical or oral antifungals or a combination of both. Topical agents are used for 1–6 weeks, according to the content of the antifungal medication. A recent meta-analysis, which included a total of 135 randomized controlled trials, showed no differences in antifungal effects, safety or tolerability among antifungal classes (Rotta et al., 2012). Terbinafine has been shown to be effective in patients with interdigital tinea pedis after only 1 week of treatment (Schäfer-Korting et al., 2008); however, patients with hyperkeratotic tinea pedis should be treated for 4 weeks. Topical ciclopirox has antidermatophytic, antibacterial and anticandidal activities and is therefore particularly effective against dermatophytosis complex (Gupta et al., 2005).

In patients with hyperkeratotic tinea pedis, antifungal medications should be applied to the bottoms and sides of the feet. Although interdigital tinea pedis may be asymptomatic, patients should apply topical drugs to the interdigital areas and to the soles of the feet because of the likelihood of plantar-surface infection. Patients tend to stop using medications after the symptoms resolve, which leads to disease recurrence. Patients may also be motivated to apply an excessive quantity of topical medications (Friedrich, 2013).

Drying agents such as potassium permanganate or Burow’s solution can be used for vesicular tinea pedis. Topical urea or other keratolytic medications can be added for moccasin-type tinea pedis (Shemer et al., 2010). If the lesions are inflamed, topical antifungal and corticosteroid combination medications can be used for a short period of time (Friedrich, 2013).
These combination drugs are more often chosen by non-dermatologist physicians than by dermatologists (Smith et al., 1998). However, patients with extensive chronic hyperkeratotic tinea pedis or inflammatory and vesicular tinea pedis typically require oral therapy, as do patients with concomitant onychomycosis, diabetes, peripheral vascular disease or immunocompromised conditions. A recent study of oral treatments for tinea pedis revealed that terbinafine was more effective than itraconazole and griseofulvin (Bell-Syer et al., 2012). Itraconazole showed interactions with other medications, including HMG-CoA reductase inhibitors, calcium-channel blockers, warfarin, cyclosporine, benzodiazepines and certain anti-arrhythmic medications. In diabetic patients, itraconazole interacted with oral hypoglycemic drugs and increased the risk of hypoglycemia. Terbinafine, however, may be a safe choice for diabetic patients (Matricciani et al., 2011). Furthermore, Ozcan et al. (2010) investigated the dermatophyte species that cause tinea pedis and onychomycosis as well as the in vitro susceptibility of these dermatophytes to terbinafine, itraconazole and fluconazole in patients with non-insulin-dependent diabetes mellitus. They reported that terbinafine was the most effective antifungal drug, whereas fluconazole was the least effective antifungal drug. They therefore suggested that terbinafine should be used for dermatophytosis in patients with diabetes mellitus.

The early diagnosis and treatment of tinea pedis would reduce the incidence of tinea unguium. Typically, this infection requires 3–12 months of treatment, rendering it more cumbersome, difficult and expensive to treat than tinea pedis (Perea et al., 2000).

Prevention and control

Although not life threatening, tinea pedis constitutes an important public health problem because of its high prevalence in risk groups and its associated morbidity. The disease can have certain negative consequences for patients, such as itching and can potentially undermine work and social lives, particularly in the aging population (Padhye & Summerbell, 2005; Weitzman & Summerbell, 1995). Tinea pedis is transferred via infected skin scales and control may be accomplished by educating infected individuals to avoid contaminating surfaces by not walking barefoot on the floors of homes or near swimming pools, public locker rooms and public showers (Gentles, 1957; Gip, 1967; Weitzman & Summerbell, 1995). Anthropophilic dermatophytes can survive at least 123 days in a chlorinated swimming pool at temperatures of 28–31°C (Fisher, 1982). Measures that can be taken to prevent tinea pedis include practicing good personal hygiene (regular washing of the feet, thorough drying and application of foot powder) and keeping the skin dry and cool at all times. The sharing of socks, slippers, shoes and towels with infected individuals should be avoided (Ilkit et al., 2005; Padhye & Summerbell, 2005; Weitzman & Summerbell, 1995). Excessive moisture and occlusion of the feet can also be reduced by wearing sandals or ventilated footwear (Padhye & Summerbell, 2005). In addition, ultraviolet treatment using an ultraviolet C sanitizing device and ozone gas reduce the fungal burden in shoes (Ghanouni et al., 2012; Gupta & Britnell, 2013).

Textiles (e.g. socks, towels and bed linens) in contact with infected skin can serve as carriers of a fungus (Bonifaz et al., 2013; Hammer et al., 2012); conversely, antimicrobial fabrics may contribute to controlling dermatophytes (Hammer et al., 2012). Trichophyton rubrum can be transferred from contaminated to non-contaminated textiles during storage in a laundry basket and during the domestic washing procedure at 30°C; however, washing at 60°C eliminates T. rubrum (Hammer et al., 2011). The high prevalence of occult tinea pedis (up to 55.1%) warrants antifungal treatment strategies for the prevention of tinea pedis in the community (Perea et al., 2000).

Conclusion

In the last five decades, tinea pedis has become a worldwide epidemiological and economic problem with the predominance of T. rubrum. The chronic and contagious nature of tinea pedis means that it will continue to be a medical concern in the twenty-first century. This review highlights the discovery, evolution, causes of spread and reproduction of the two major etiological agents of tinea pedis, T. rubrum and T. mentagrophytes sensu lato. Accurate clinical data, including the appropriate diagnosis of the clinical forms of tinea pedis and the reliable identification of the causative fungus, will improve the education and knowledge of medical practitioners in the field. Molecular tools, such as nested PCR, improve the consistency and quality of diagnoses and patient care and are required to obtain clues regarding the source of infection. Treatment not only improves the symptoms of tinea pedis but also prevents the risk of spread to other regions of the body, thus reducing local and systemic complications. Although tinea pedis constitutes one of the most frequent infectious diseases in man, specific measures for its control have been exercised only sporadically until now. Further studies with emphasis on applying modern taxonomic concepts in a clinical context will enhance our current understanding of the field.

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