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Widespread dermatophytosis in a healthy adolescent: the first report of multidrug-resistant *Trichophyton indotineae* infection in the UAE

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Abstract

A multidrug-resistant dermatophyte species recently arose in India, first described as terbinafine-resistant *Trichophyton interdigitale* and soon given a separate name: *T. indotineae*. Thanks to its treatment recalcitrance, person-to-person spread, and frequent travel, before long it was identified in many countries on all continents. We describe here the case of a boy with widespread, extremely pruritic, inflammatory dermatophytosis affecting his face, neck, trunk, and extremities, unsuccessfully treated for months with oral terbinafine and fluconazole and a range of topical antimycotics. Qualitative polymerase chain reaction of skin scrapings from his lesions identified a *T. interdigitale* complex fungus, highly probably *T. indotineae* due to conspecificity and antifungal resistance. Oral itraconazole, administered over 8 weeks, cleared the infection. Because the patient had not traveled outside the United Arab Emirates for months before the infection became obvious, it must have been acquired from a local source.

Keywords: case report, superficial fungal infections, drug-resistant dermatophytes

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Introduction

Over the past decade, there have been a growing number of reports of symptomatic and treatment-recalcitrant tinea, initially from India, and later from other parts of Asia and Europe. The infection is caused by *Trichophyton indotineae* (early on recognized as *T. interdigitale* complex isolates, then as *T. mentagrophytes* genotype VIII), originally a zoophilic species that has now acquired an anthropophilic mode of infection (1, 2). It is commonly resistant to terbinafine, but resistance to other antifungals is growing as well (3, 4). Easy and widespread travel has clearly facilitated the rapid spread of this fungal species to all continents.

Case report

A 15-year-old male was seen for a 5-month history of a widespread extremely pruritic eruption treated over that period with topical and oral terbinafine, oral fluconazole, topical antimycotics, topical tacrolimus, and oral antihistamines. Despite treatment with multiple medications, the lesions grew in both size and number. The three other members of the patient's family were clinically unaffected at the time of his diagnosis. The patient had only traveled to Europe during his summer vacation. The first lesion appeared on the right groin. Over the 5-month period, the lesions spread to affect his face, neck, upper extremities, trunk, thighs, and buttocks. There was no history of sexual activity or contact with another individual with visible skin lesions. No samples were previously obtained prior to the empirical treatments he received.

On examination, ring-shaped, coalescing erythematous plaques with peripheral scales, some resembling pityriasis rosea and others the pseudoimbricata type, were found in the groin area bilaterally, and on the inner thighs, buttocks, trunk, extensor upper arms, neck, and face (Fig. 1a–c). Scrapings were obtained for native microscopy and PCR amplification for dermatophytes, and a punch biopsy of the annular plaque on the thigh was carried out. KOH microscopy confirmed the presence of branching hyphae. PCR (PN-401/402 DermaGenius® 2.0 Complete Multiplex real-time PCR kit) detected sequences of the *T. interdigitale* complex,

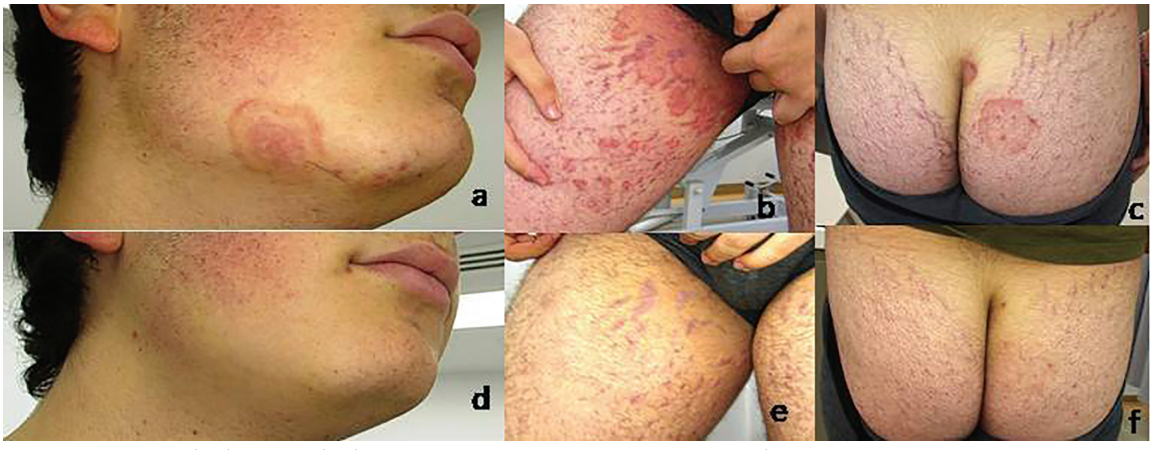

Figure 1 | Cutaneous lesions before (a–c) and after (d–f) treatment, affecting the right mandibular area (a and d, displaying a pseudoimbricata appearance), upper inner thigh (b and e), and right buttock (c and f).

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which also contains the *T. indotineae* species; further characterization of the internally transcribed sequences (ITS) specific for *T. indotineae* was not performed. However, genetic relatedness among the genomes of the two strains, confirmed by the FastANI value of 98.75%, is enough to indicate conspecificity (5). Furthermore, clinical features and resistance to oral terbinafine and fluconazole further indicated that the infection might be caused by the highly resistant strain of *T. indotineae*. The histopathologic study confirmed cutaneous fungal infection with a prominent inflammatory reaction (Fig. 2).

We initiated treatment with oral itraconazole (200 mg daily for 8 weeks) along with topical clotrimazole. Within a week, the pruritus significantly decreased. Seven weeks into the treatment, all lesions fully resolved (Fig. 1d–f).

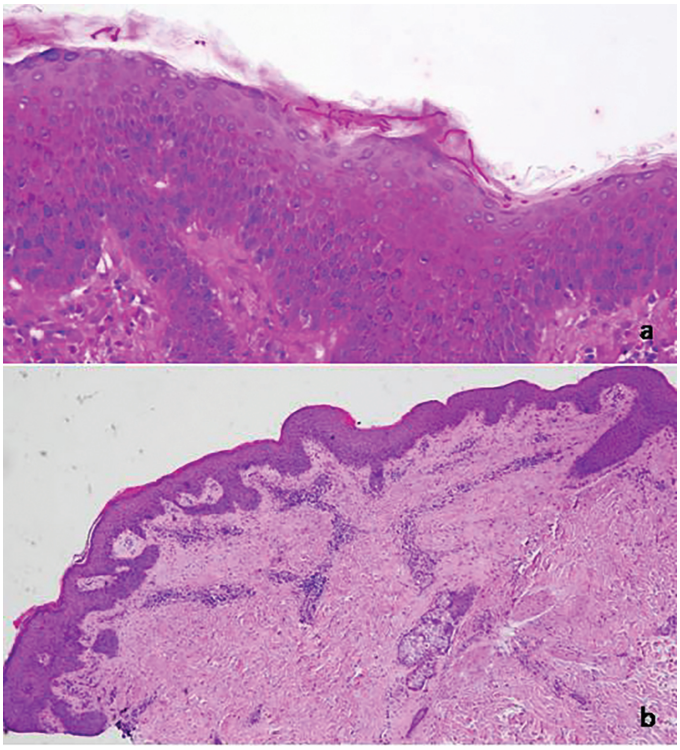

Figure 2 | Histopathology revealed (a) numerous fungal hyphae in the stratum corneum (H&E, original magnification ×100) and (b) abundant inflammatory infiltrate across the papillary and reticular dermis (H&E, original magnification ×40).

Discussion

Superficial skin infection caused by *T. indotineae* (initially defined as resistant *T. interdigitale*) has introduced a new dimension in the management of dermatophytosis (2). Due to widespread and indiscriminate use of (over-the-counter) topical antimycotics combined with corticosteroids and antibiotics, India has been affected by an ongoing outbreak of severe and treatment-resistant infection by *T. indotineae* since 2014 (1–4). The fungus proved to be highly resistant to terbinafine due to point mutations of the squalene epoxidase gene (*SQLE*). Since then, the species has spread to other Asian countries, reaching Europe and North America by 2019 (3, 6). Travel, immigration, and subsequent local transmission will make the problem even greater over the coming years.

Clinically, the infection usually affects large surfaces on the trunk, groins, extremities, and face (tinea corporis, tinea cruris, and tinea faciei) accompanied by severe pruritus and burning. A number of patients have also described pain (4). Fingernails are rarely a site of infection because *T. indotineae* has poor keratolytic activity. The morphology of the lesions varies from papulosquamous, pityriasis rosea-like, pseudoimbricata, and pustular to lichenoid (4, 7). Although oral itraconazole is generally effective in eradicating the infection, reports of itraconazole resistance are emerging (8). This may make the treatment of *T. indotineae* very challenging in daily practice. Newer safe antifungals active against the fungus, such as orolofim, are waiting for official approval (9). Although many topical antimycotics are effective against *T. indotineae*, such as miconazole, clotrimazole, luliconazole, ciclopirox olamine, and voriconazole, their use is impractical in widespread infections, which are common (4). There are reports of successful use of high doses (500 mg daily) or prolonged treatment (up to 4 months) with terbinafine or oral voriconazole, although the latter has more potential side effects (10, 11). Albeit rarely, some strains of *T. indotineae* may be sensitive to terbinafine (7).

Conclusions

This report is aimed at raising awareness of the ongoing spread of a strain of *T. indotineae* resistant to common oral antifungals outside of India. Widespread, inflammatory, and highly symptomatic tinea not responding to standard treatment should alert a dermatologist to consider recalcitrant dermatomycosis in the differential diagnosis. Not only should dermatologists be aware of this pathogen, but local laboratories must be prepared to identify this multidrug-resistant fungus and offer antifungal susceptibility testing. The most common *SQLE* mutations may be detected by commercially available PCR tests (12).

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