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Advances in Microbiology, Infectious Diseases and Public Health: Refractory *Trichophyton rubrum* Infections in Turin, Italy: A Problem Still Present

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Abstract

Dermatophytosis caused by *Trichophyton rubrum* is the most common cutaneous fungal infection in industrialized countries and worldwide with high recurrence and lack of treatment response. In addition, patients with cutaneous and concurrent toenail lesions are often misdiagnosed and therefore treated with an inappropriate therapy. In this study, we evaluated five previously misdiagnosed cases of *T.rubrum* chronic dermatophytosis sustained by two variants at sites distant from the primary lesion. Our patients were successfully treated by systemic and topical therapy, and 1 year after the end of therapy follow-up did not show any recurrence of infection.

Our data indicate that the localization of all lesions, the isolation and the identification of the causative fungus are essential to establish the diagnosis and the setting of a correct therapeutic treatment to avoid recurrences.

Keywords

Trichophyton rubrum • Chronic dermatophytosis • Misdiagnosis

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Chronic dermatophytosis is a condition in which the clinical symptoms persist for more than 1 year with episodes of exacerbation and remission (Hay 1982; Zaias and Rebell 2003; Prasad et al. 2005). The main etiologic agent is *Trichophyton rubrum* responsible for 90 % of chronic infections (Di Chiacchio et al. 2014; Nenoff et al. 2014). Chronicity is probably related both to fungal cell wall components, such as mannan, that play an important role in the process of down-modulation of cell-mediated immune response of the host and to a lack of treatment response (Blake et al. 1991; Sato and Tagami 2003; Waldman et al. 2010). Patients with cutaneous and concurrent toenail lesions are often misdiagnosed and, therefore, treated with an inappropriate therapy (Larruskain et al. 2005).

In this study, we evaluated previously misdiagnosed cases of *T.rubrum* chronic dermatophytosis in five patients admitted to the Medical Sciences Department, University of Torino (Italy), through an investigation of clinical and mycological infection aspects.

Case 1 A 42-year old male, born in Ecuador, reported a 7-year history of itchy and squamous lesions on the soles, toenails, palms and the nail plates, before arriving in Italy (Fig. 1a–d). Despite therapies with topical antibacterial agents in his native country, the patient had extensive erythema with painful papules, pustules and crusts in the chin and beard (Fig. 1e, f). Incomplete alopecia, associated with follicular nodules most prevalent above the upper lip was seen. Hands and fingernails examination revealed hyperkeratosis and distal onycholysis.

Case 2 A Caucasian male of 48 years presented erythematous and squamous lesions on the feet and toenails. A closer examination revealed scaling lesions on the inguinal area and buttocks, hands and fingernails plate hyperkeratosis and distal onycholysis.

Case 3 A Caucasian female of 78 years reported a 2-week history of extensive erythema with papules and fine pustules appearing at the opening of hair follicles in the inguinal region (Fig. 2a, b). An intense erythema involved both buttocks and thighs (Fig. 2c). Examination of the left foot revealed sole and toenail/fingernail hyperkeratosis, with nail plate thickened, friable and yellowish (Fig. 2e, f). The left knee (Fig. 2d) and the right leg were also involved with flaking in net margins.

Case 4 A Caucasian female of 69 years, with rheumatoid arthritis, treated for 20 years with therapeutic cycles of methotrexate (7.5 mg/week) and prednisone (5 mg/day), presented a chronic erythematous scaly dermatitis extended to the lower back and rear thigh area, diagnosed as psoriasis (Fig. 3e). Since 2006, she was treated with emollient cream and topical steroids without benefit. On physical examination, the patient revealed *tinea pedis* and *tinea unguium* with sole and toenails plate hyperkeratosis (Fig. 3a, b), squamous lesions on the elbow, on the back and left palm (Fig.3c, d, g). Involvement of the scalp with flaking dandruff and thinning hair was observed (Fig. 3f).

Case 5 A Caucasian female of 68 years, with rheumatoid arthritis, treated for several years with prednisone (25 mg/day), presented a history of chronic erythematous scaly dermatitis diagnosed as psoriasis and treated with emollient cream without benefit. A closer examination revealed an intense lamellar desquamation of the toenails and fingernails, hyperkeratosis of the soles and the palms, scaling lesions with sharp margins in the breast, abdomen, inguinal area, buttocks and thighs, neck and chin.

Mycological analysis of all patient lesions was performed. Skin and nail samples were collected, examined under a light microscope (20 % KOH + 40 % DMSO preparation) and inoculated into Mycobiotic agar (Merck, KGAA, Germany) to detect dermatophytes. Molds identification was based on macroscopic and microscopic characters of the colonies after 15 days of incubation at 25 °C.

All patients had dermatophytosis and concurrent lesions caused by two variants of *T.rubrum*:

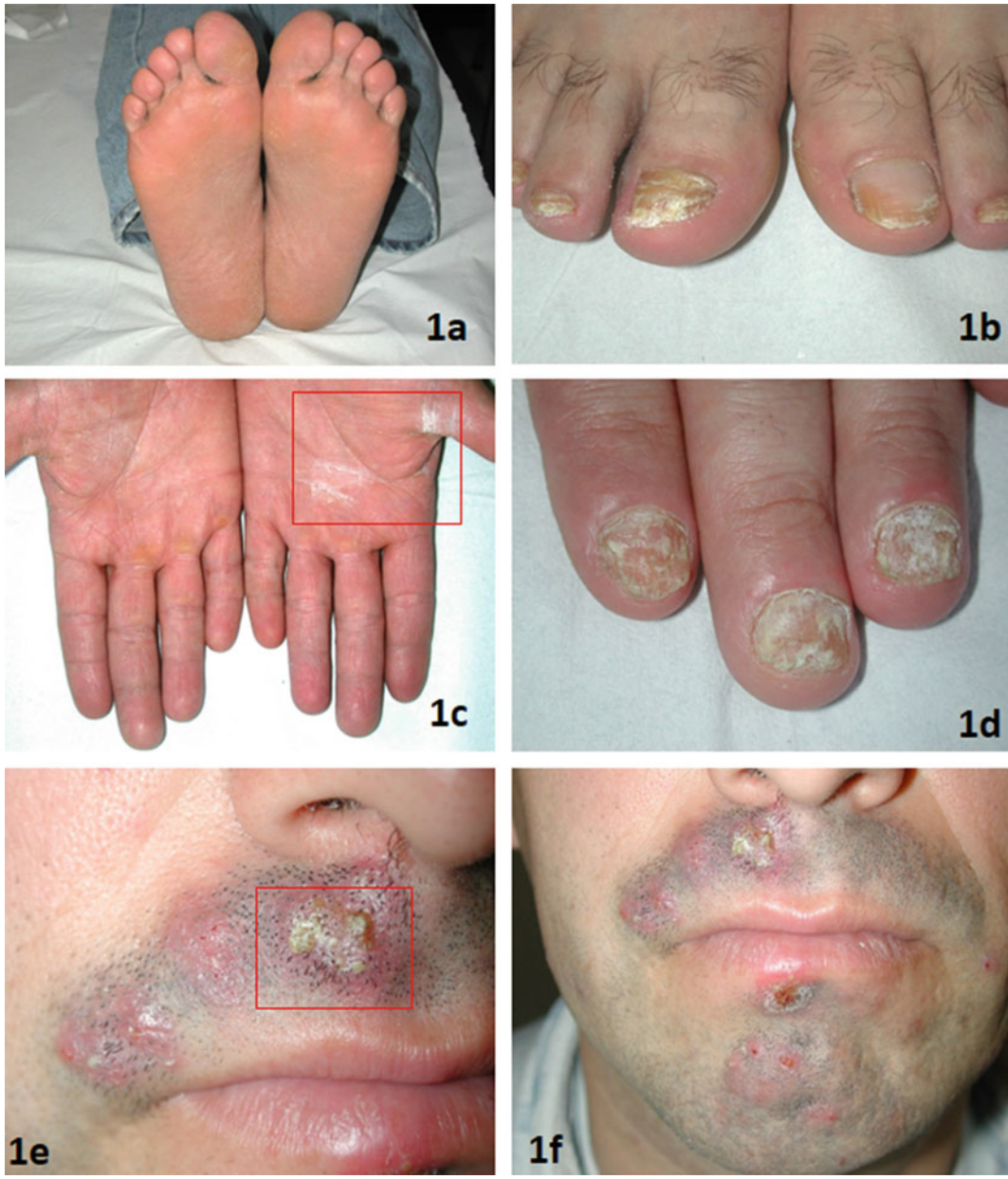

Fig. 1 Case 1. A 42-year old, male, born in Ecuador. Squamous lesions on the soles, toenails, palms and nail plates (**a**–**d**); extensive erythema in the chin and beard with follicular nodules above the upper lip (**e**, **f**)

downy white-colored colonies with reverse pigment brownish-yellow (Cases 1, 2, and 3) or deep wine-red (Cases 4, and 5). Scant teardrop-shaped microconidia along septate hyphae were observed on microscopic colonies examination.

The primary lesion was localized always in the foot (*tinea pedis*), in agreement with other studies (Larruskain et al. 2005). Secondary lesions distributed in other sites were the main demand for medical consultation: in all five cases, the anatomical sites mainly interested were the inguinal area, buttocks, palms and fingernails (*tinea unguium*). In only one case, *tinea capitis* was observed (Case 4). Patient

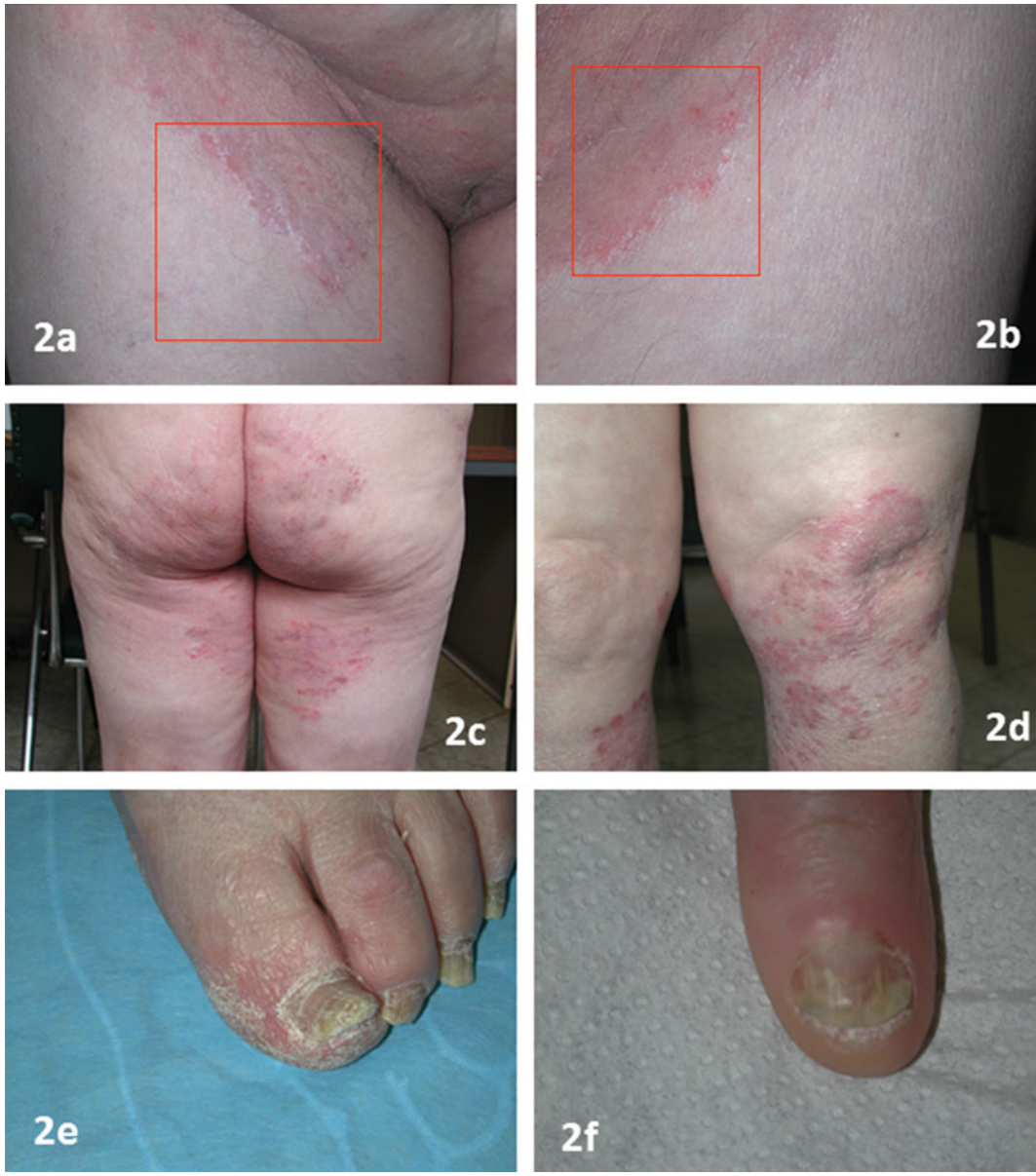

Fig. 2 Case 3. A 78-year old, female, Caucasian. Extensive erythema with papules at the opening of hair follicles in the inguinal region (**a**, **b**), buttocks and thighs (**c**); left knee with flaking in net margins (**d**); toenail and fingernail hyperkeratosis (**e**, **f**)

4 under methotrexate therapy and patient 5, under corticosteroid therapy had risk factors predisposing them to fungal spread. *Tinea* in such cases tends to be chronic and extended, mimicking various skin diseases, such as psoriasis, eczema, etc., as in Patients 4 and 5 (Atzori et al. 2012; Tan et al. 2014).

For all patients a successful treatment with topical (azoles) and systemic (terbinafine hydrochloride 250 mg/day) antimycotics was carried out. In details, in patient 1, after 4 weeks of treatment, all skin lesions were completely healed and culture results were negative; both direct mycological and culture were negative

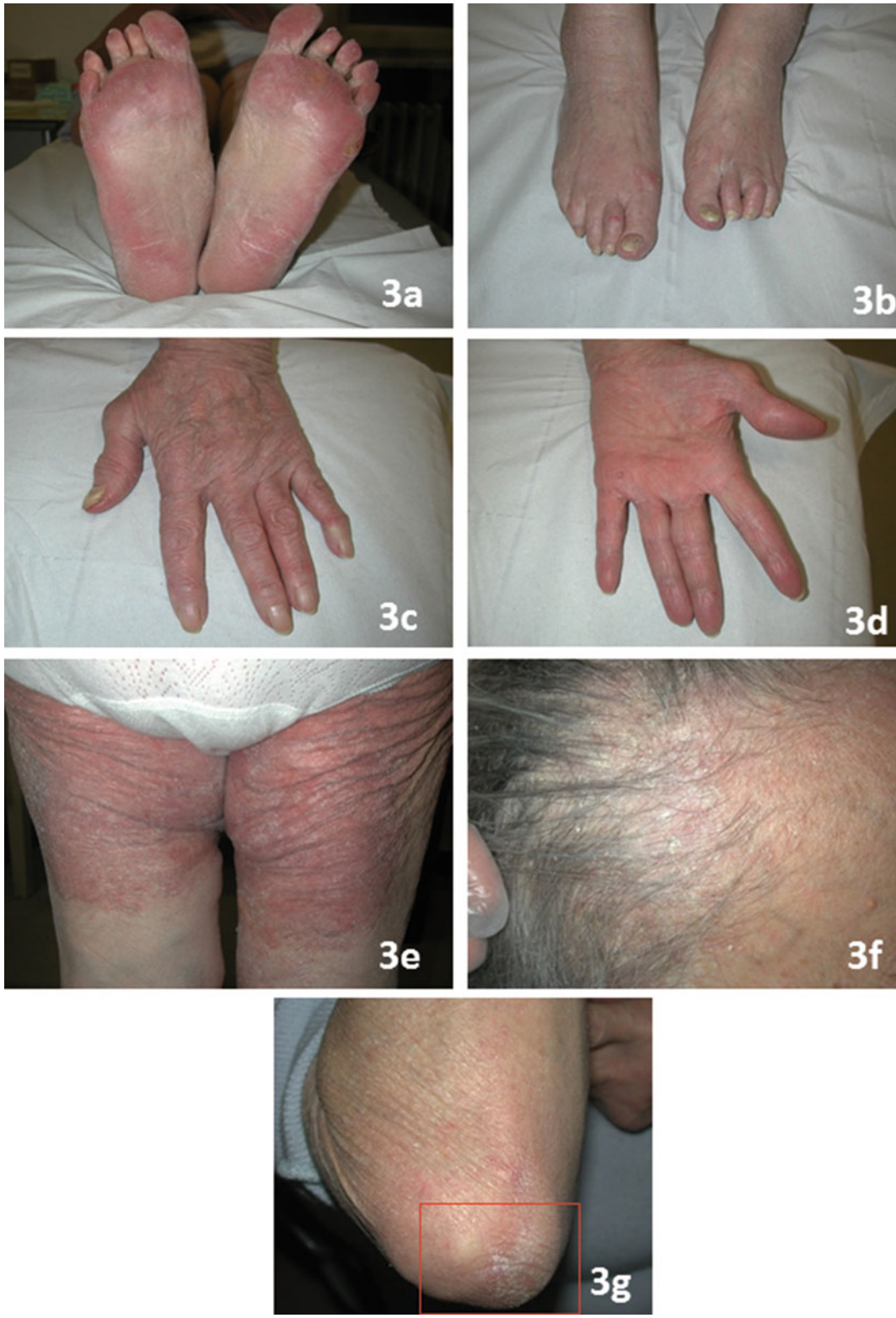

Fig. 3 Case 4. A 69-year old, female, Caucasian, with rheumatoid arthritis. Sole and toenails hyperkeratosis (**a**, **b**); back and left palm squamous lesions (**c**, **d**); extensive erythema on lower back and rear thigh area diagnosed as psoriasis (**e**); scalp with flaking dandruff and thinning hair (**f**); squamous lesions on the elbow (**g**)

also for nails after 3 months. In patient 2, all lesions were completely healed and culture results were negative after 12-weeks of treatment. In patient 3, all skin lesions were completely healed after 6 weeks of treatment; both direct mycological and culture were negative for nails after 4 months. In patient 4, after 4-weeks of treatment, all skin lesions were completely healed; both direct mycological and culture were negative also for nails and scalp after 5 months. In patient 5, after 6-weeks of treatment, all skin lesions were completely healed and culture results were negative; the nail lesions were alleviated after 5-months therapy.

The five clinical cases reported in this study are considered dermatophytosis, affecting both immunocompetent and immunodeficient patients, and fulfilled the diagnostic criteria of *T.rubrum* chronic dermatophytosis, as indicated by the literature (Zaias and Rebell 1996; Böhmer and Korting 1999; Kick and Korting 2001; Balci and Cetin 2008; Piñeiro et al. 2010; Kong et al. 2015). Since in our group of patients from the beginning a correct therapeutic treatment was not carried out or misapplicated, a gradual spread of the infection occurred to the toenails, as secondary site involved, constituting the reservoir of infection that spread later to other sites, such as legs, groin, hands, face and scalp. On the other hand, it has to be underlined that *tinea unguium* is an infection usually more resistant to treatment, whose eradication is difficult even with appropriate therapy (Gupta and Cooper 2008).

For fungal infection eradication, diagnosis must be based on both a correct patient history and an adequate microbiological study that includes the identification of the species isolated. Therefore, it is essential a careful examination of the patient *in toto* to avoid inappropriate or wrong therapeutic treatment. In fact, as in the first patient, the antibiotic treatment was established solely on the observation of highly inflammatory facial injuries that did not present the typical clinical features of *T.rubrum* infection (Yin et al. 2011); hence, the treatment being wrong was ineffective.

In conclusion, our data indicate that in all cases of suspected syndrome or when skin involvement is extended to multiple sites, the localization of all lesions, the isolation and the identification of the causative fungus are essential to establish the diagnosis, prognosis and the setting of a correct antifungal therapy to avoid recurrences.

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