



Congenital ichthyosis associated with *Trichophyton rubrum* tinea, imitating drug hypersensitivity reaction



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ABSTRACT

Tinea corporis and congenital ichthyoses are common dermatological diseases. The association of the two disorders is plausible due to the immunological and barrier defects of ichthyoses; however, relatively limited literature is available in this field. Since superficial fungal infections possess atypical morphology in keratinization disorders, and could imitate other dermatological conditions, the correct diagnosis can be challenging. We present the case of a 54-year-old woman with ichthyosis, who was initially treated for drug-hypersensitivity reaction.

1. Introduction

Both tinea corporis and ichthyoses are relatively common clinical entities. Congenital ichthyoses are disorders of keratinization, accompanied by increased cell turnover, damaged skin barrier, and immunological dysfunctions, which make the skin vulnerable to infections. The skin of patients with ichthyosis is dry, thickened, accompanied with massive scaling. Widespread erythema could be also present. Due to these symptoms, the diagnosis of other, concurrent skin disorders-including tinea corporis-may be difficult, since they are often atypical in presentation [1,2].

Although an elevated rate of fungal infection is expected with ichthyoses, relatively few articles have been published related to the association of the two disorders, and a vast majority of them are pediatric reports. To avoid inadequate treatment, in particular administration of corticosteroids (topical and oral), previous reports recommended that in patients with ichthyosis fungal infection should be suspected in case of a sudden, widespread erythroderma [1].

In this article, we present a clinical case of ichthyosis that was misdiagnosed as drug-hypersensitivity reaction, and review the pathomechanism and treatment options of ichthyoses-associated tinea corporis.

2. Case presentation

We present the case of a 54-year-old woman with ichthyosis. She

had been taking acitretin (25 mg/day, for ichthyosis) for decades. Her skin symptoms were moderate. In January 2018 she developed urticariform erythematous skin symptoms (day 0) and was put under observation at the local internal medicine department (day +10) (Fig. 1 a). Six months before the skin symptoms, warfarin treatment has been started because of deep vein thrombosis (day -180). Because drug hypersensitivity reaction was suspected, warfarin was changed to low-molecular-weight heparin (enoxaparin sodium) and systemic prednisolone (1 mg/kg/day) and topical clobetasol propionate were initiated (day +14). After modest improvement; however, her skin symptoms became more severe.

One month after the onset of skin symptoms the patient was admitted to our department with widespread erythematous plaques and pustules (day +35) (Fig. 1 b-d). Laboratory parameters revealed only modest alterations, including elevated CRP (22.2 mg/l) and erythrocyte sedimentation rate (34.0 mm/h). Lymphocyte transformation test (LTT) was performed to exclude drug-hypersensitivity reaction. LTT showed no positivity to warfarin, and autoimmune serologies were negative. *Staphylococcus aureus* and *Staphylococcus haemolyticus* were cultured from the pustules.

Although dermatophytes were not identified by the culturing of pustules, the clinical picture raised the possibility of superficial fungal infection. Therefore a skin biopsy and mycological sampling were carried out. Native fungal preparation and periodic acid-Schiff (PAS) staining both indicated the presence of fungal filaments (Fig. 2 a). Moreover, *Trichophyton rubrum* was identified from the mycological

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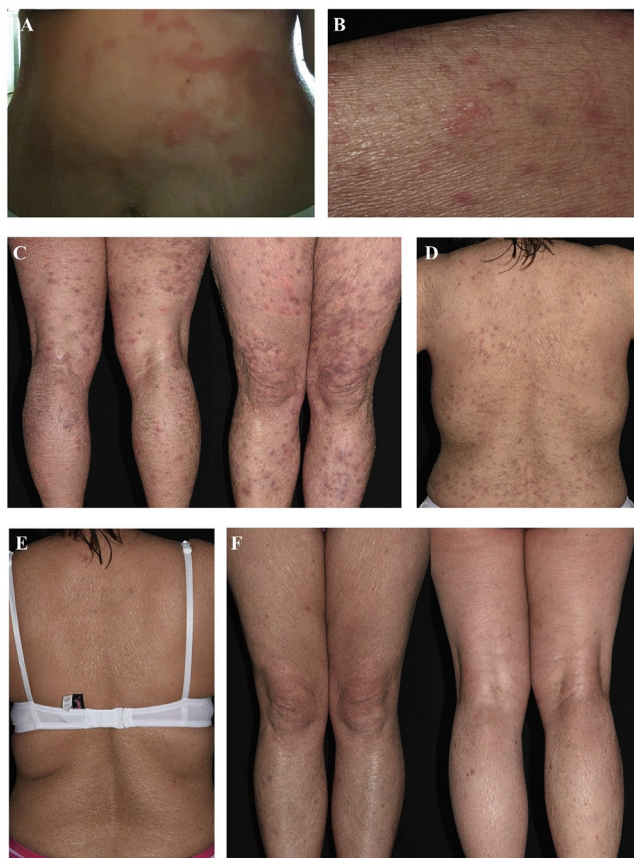


Fig. 1. (A) initial erythematous, urticariform skin lesions (photographed by the patient) (B) pustule and papules/plaques on the arm upon admission of the patient, 1 month after the beginning of the symptoms (C–D) circumscribed, erythematous, slightly scaling lesions of the lower extremities and the trunk (E–F) regression of skin symptoms after 2 months of oral terbinafine treatment (250mg/day).

culture (Fig. 2 b). Although the patient did not have typical signs of a fungal nail infection, *Trichophyton rubrum* was also present in nail scrapings. No other family member complained about skin or nail symptoms.

Based on the result of microbiological sampling, oral terbinafine (250 mg/day) and topical antimycotics were started (day +44). One month after the initiation of the therapy significant improvement was achieved (day +74). The treatment was continued for a total of 3 months, when only mild symptoms of ichthyosis remained (day +134) (Fig. 1 e-f).

3. Discussion

Tinea corporis is classically defined by scaling and circumscribed erythematous plaques. However, in patients with ichthyosis symptoms can be deceptive. This may result in misdiagnosis, since the symptoms mimic the clinical picture of drug-hypersensitivity reaction and papulosquamous skin disorders. Hoetzenecker et al. reported an ichthyosis vulgaris-associated case, which was first considered as a newly onset psoriasis or neutrophilic dermatosis Sweet syndrome [2]. Other reports claimed that the right diagnosis -congenital ichthyosiform erythroderma associated *Trichophyton rubrum* infection-in the background of a pustular erythroderma was revealed only with a 2,5 years delay [3]. As in case of our patient, the atypical symptoms were misdiagnosed as drug-hypersensitivity reaction, and an inadequate therapy (systemic and topical corticosteroid treatment) was started at the internal medicine department.

Altered keratinocyte turnover, defects in cell-mediated cutaneous immunity and escape mechanisms of *Trichophyton rubrum* all facilitate mycoses in ichthyoses [2,4]. It is well known that the thickened but dysfunctional skin barrier promotes pathogen colonization. One of the main virulence factor is the keratinase activity of the *Trichophyton spp.* This hyperkeratotic epidermis of ichthyotic skin is a nutritive microbiological environment for the dermatophytes. In addition, the fungal cell wall component mannan regulates cell-mediated immunity and proliferation of keratinocytes [4]. The impairment of cellular immunity, Th1/Th2 imbalance, is the characteristic feature of the host organism which makes it susceptible to fungal infections. In certain types of ichthyoses, Th2 dominance and atopic predisposition is particularly pronounced including the most common ichthyosis vulgaris and the ichthyosis syndrome Netherton [2,4–7]. Macrophage dysfunction may also play an important role in the development of the disease [2,4]. Finally, during the clinical observation of widespread tinea (also in case of ichthyoses associated forms), exclusion of immune deficiency is always important [2].

The most frequent pathogen is *Trichophyton rubrum*, responsible for 80–93% of recurrent or chronic dermatophyte infections [2]. Other *Trichophyton spp.* and *Candida albicans* may also be involved [8–12]. One of the first documented cases was related to *Trichophyton mentagrophytes*, while other reports indicated the pathogenic role of *Trichophyton verrucosum* or non-albicans *Candida* species [8,9,11]. Onychomycosis or cross-infections from family members may serve as sources of mycoses. Shelley et al. and Scheers et al. reported pediatric cases where the parents' onychomycosis led to skin infections in children with ichthyosis [3,4].

To prevent recurrences, a longer (2–3 months) course of the fungicidal terbinafine is recommended as the first choice of therapy in the event of *Trichophyton* infections. The effectiveness of terbinafine is based on its fungicidal activity, accumulation in stratum corneum and capacity to penetrate deeper in the skin and skin appendages [1–5]. However, a case of the inefficacy of oral terbinafine treatment has also been reported [13]. Terbinafine resistance was verified by the EUCAST E.Def 9.3 method (MIC: 4 µg/mL; normal range: < 0.03 µg/mL) while antifungal susceptibility testing to azoles indicated the effectiveness of these compounds. 100mg/day systemic itraconazole proved to be a suitable alternative medication [13]. In addition, case with a Darier disorder and a patient with onychomycosis described a terbinafine resistant dermatophytosis [14,15]. Molecular backgrounds for terbinafine resistance are squalene-epoxidase point mutations and multiple copies of *salA* gene [13,16,17]. Other squalene inhibitors are also ineffective because of the same molecular alterations. Even with these reports of resistance, terbinafine is the most effective drug against *Trichophyton spp.*, followed by the triazole itraconazole. Alternative drugs such as griseofulvin and imidazoles are less effective [4,5]. Taken together, susceptibility testing is indicated by recurrent ichthyosis-associated tinea corporis.

Besides antifungal agents, treatment of the underlying skin disorder is also indispensable. Skin hygiene, regular bathing and usage of moisturizers are the basis of prevention. In addition, keratolysis is essential to inhibit fungal colonization and invasion. In certain types of ichthyoses, oral retinoid treatment is also required to control cell turnover and desquamation [5].

In summary, the recognition of ichthyosis-associated tinea corporis is a challenge even for experienced dermatologists. In order to avoid chronic dermatophytosis and superinfections, adequate diagnostic steps should be taken, and effective therapy must be started as soon as possible. We also emphasize a careful and detailed examination of the skin and appendages, taking of mycological samples of all sites (including nail scrapings) and checking for symptoms of tinea infection in family members to prevent recurrent infections. Regarding antifungal treatment, 2 or 3 months of systemic terbinafine is the first choice. In therapy resistant cases, itraconazole could be an effective alternative.

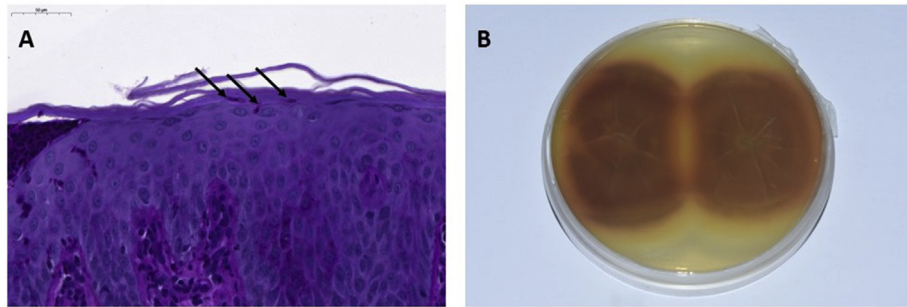


Fig. 2. (A) fungal filaments demonstrated by PAS staining in skin biopsies (B) *Trichophyton rubrum* cultured on Sabouraud dextrose agar with cycloheximide (the culture plate is pictured from the reverse).

Declaration of competing interest

There are none.

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There are none.

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