

Eczema with hypersensitivity to fungal allergens in patients with onychomycosis

Wyprysk oraz nadwrażliwość na alergeny grzybicze wśród pacjentów z grzybicą paznokci

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Abstract

Fungal pathogens can cause different forms of allergy. However, there are limited literature data, if the fungi, which are found in nails, could exacerbate the allergic skin diseases. Here we presented three patients who suffered from eczema, predominantly localized on the lower legs. Moreover, they all had onychomycosis within toenails and in all patients hypersensitivity to fungal allergens was observed. In all patients the standard treatment of eczema was poorly effective. However, the introduction of anti-mycotic agents resulted in significant improvement of skin symptoms. Based on the presented patients with eczema we could hypothesize, that in some patients the skin allergic diseases could be exacerbated or even provoked by fungal allergens found in the nails.

Key words: eczema cruris, onychomycosis, allergy, fungal allergens

Streszczenie

Patogeny grzybicze mogą powodować różne formy chorób alergicznych. Jednakże dane z piśmiennictwa na temat, czy grzyby odpowiedzialne za zmiany paznokciowe mogą przyczyniać się do zaostrzenia skórnych chorób alergicznych, są skąpe. W niniejszej pracy zaprezentowano troje pacjentów z wypryskiem zlokalizowanym głównie w zakresie podudzi. U wszystkich stwierdzono również współistnienie grzybicy paznokci stóp, a wykonane testy skórne potwierdziły nadwrażliwość na alergeny grzybicze. U wszystkich pacjentów standardowa terapia zmian wypryskowych wykazywała niską skuteczność, natomiast dołączenie do leczenia leków przeciwgrzybiczych skutkowało znaczącą poprawą stanu klinicznego skóry. Na podstawie obserwacji własnych i danych literaturowych można sugerować, że u niektórych osób alergeny grzybów wywołujących grzybicę paznokci mogą przyczyniać się do zaostrzenia, a nawet indukcji skórnych chorób alergicznych.

Słowa kluczowe: wyprysk podudzi, grzybica paznokci, alergia, antygeny grzybicze

Introduction

The pathogenetic fungi could be responsible not only for infections but also for allergic reactions caused by the exposition to fungal allergens. *Candida* sp. and *Malassezia* sp. are the most important pathogens in the induction of fungal allergy and could be responsible for allergic rhinitis, allergic sinusitis, atopic asthma, urticaria or allergic eczema (1-5). The importance of hypersensitivity to fungal allergens has been mostly underlined in patients suffering from atopic dermatitis (AD), in whom fungal allergens could provoke exac-

erbations (3-6). The employment of antifungal drugs in AD patients with proven hypersensitivity to *C. albicans* and *M. furfur* resulted in significant reduction of total serum level of IgE as well as the level of specific to these allergens IgE fractions (7). Although onychomycosis is a frequent condition in human population, the problem of hypersensitivity to fungal allergens found in the nails has rarely been described (8, 9). Therefore, here we present three patients suffering from eczema, who also presented with toenail onychomycosis and demonstrated hypersensitivity to fungal allergens in skin prick tests. Moreover, significant clinical improve-

ment of eczematous lesions was observed after introduction of antifungal agents.

Case reports

Case 1

A 47-year-old male patient was admitted to our department because of recurrent, resistant to therapy eczema of the lower legs. First skin lesions appeared 12 years ago on the dorsal surface of the feet. Initially the skin lesions were satisfactory controlled with potent topical steroids. However, for the last 2 years the skin lesions have become more extensive and more difficult to treat – the skin lesions only partially responded to topically applied corticosteroids and the exacerbations were observed immediately after discontinuation of such treatment. The atopic history of patient as well as among his relatives was negative.

On admission the patient presented with erythematous, partially lichenified and itchy patches on the lower legs, with multiple excoriations and scaling (fig. 1 and 2). Similar, but less intensive skin lesions were also observed on the back and on upper arms. Moreover, all toenails were yellowish and thickened (fig. 2). Additionally, onycholysis with subungual hyperkeratosis in the left great toe was noted (fig. 3). Fingernails were unchanged. The patient was not able to say, how long the nail lesions have been present within toenails.

Laboratory investigations revealed elevated total serum level of IgE (1976 U/cm³). Other routine laboratory tests were within the normal range (blood smear, urine examination, biochemical markers of kidney and liver function, serum glucose level). The direct mycological examination revealed yeast-like fungi present in the nail specimens. Although the mycological culture of the nail specimens was negative, the patient demonstrated hyperreactivity to *C. albicans* allergens found in skin prick tests (fig. 4). The reaction to other fungal allergens (*Alternaria alternata*, *Rhizopus nigricans*, *Penicillium notatum*, *Aspergillus fumigatus*, *Botrytis cinerea*) as well as patch tests with standard contact allergens were all negative.

Based on the clinical manifestation and laboratory results the eczema provoked by fungal allergens found in nail plates was suspected. Itraconazole pulse therapy (200 mg twice daily for 7 days) supported by topical antimycotics (1% clotrimazole) and corticosteroids (0.05% betamethazone dipropionate) was started. Although a rapid improvement of skin lesion within the first 10 days of treatment was observed, after discharge from the department the patient discontinued the treatment (therefore only one pulse of itraconazole was taken) and recovery of skin lesions was noted.

Case 2

73-year-old male patient, with negative personal and family atopic history was admitted to our department in order to diagnose and treat disseminated eczema. The patient has been suffered for 4 years from insulin-independent diabetes mellitus. The skin disease started 3 years ago. Initially the patient suffered only from extensive pruritus without any visible skin lesion. Pruritus poorly responded to antihistaminic drugs and topical emollients. First skin lesions appeared 2 months prior to current admission.

On admission the patient presented with multiple papules, erythematous patches and fissures, predominantly localized on the lower legs (fig. 5). Less intensive skin lesions were also present on the upper legs. The skin lesions were accompanied by itching and multiple excoriations due to intensive scratching. Moreover, distal and lateral onycholysis with subungual hyperkeratosis was seen within great toenails (fig. 6). Additionally, macerations of epidermis in interdigital space were observed.

In laboratory examinations the total serum IgE level was significantly elevated (17968 U/cm³) as well as absolute count of eosinophils in peripheral blood (836/mm³). No parasites were stated in stool. The direct mycological examination of specimens obtained from great toenails as well as from interdigital space revealed a presence of fungal hyphae. The skin prick tests demonstrated positive reaction to *Trichophyton mentagrophytes* allergens and slightly positive to *C. albicans* (fig. 7). The remaining prick tests were negative. As it was suspected the skin lesions were related to hyperreactivity to *T. mentagrophytes* allergens, the treatment consisting of terbinafine 250 mg/day orally with topical corticosteroids and emollients was introduced. The significant clinical improvement was observed after 2 weeks and the patient is free of symptoms 3 months after the therapy was started.

Case 3

A 52-year-old male patient, with no history of atopic disorders, was admitted to our department due to the diagnosis and therapy of disseminated eczema. First symptoms appeared 10 months before admission on the back. The skin lesions were erythematous and itchy. On admission the whole body surface was covered with small to larger erythematous skin lesions. In some lesions small erosions were observed. The toenails have been thickened, yellowish and with subungual hyperkeratosis for over twelve months. In laboratory examinations elevated total serum level of IgE (626 U/cm³) as well as elevated number of eosinophils (3366/mm³) in peripheral blood were stated. For eczematous skin lesions oral antihistaminic (cetirizine, loratadine) drugs and topical potent corticosteroids (flucinolone acetonide) were employed, however, without significant improvement of skin lesions and with no reduction of itch. As from nails *Candida* sp. was cultured (fig. 8 and 9), one month after discharge from the department skin prick tests with fungal allergens were performed. The examination revealed hyperreactivity to *C. albicans* and *T. mentagrophytes*. Remaining prick test were negative. The patient was advised to begin anti-mycotic treatment, however, he was lost from follow-up.

Discussion

The role of fungal allergens in allergic skin diseases has not been fully clarified yet. However, many literature data indicated the importance of this group of allergens in provoking exacerbations of AD and other allergic diseases (3-12). In Norvall and Johansson study (13) on the presence of specific to *Pityrosporum orbiculare* IgE antibodies it was shown that in 26/131 children (20%) suffering from AD these antibodies were present. Interestingly, a significant higher proportion of patients who presented *P. orbiculare* antibodies had current eczema than those without detectable IgE anti-



Fig. 1. Case 1: Erythematous, itchy skin lesions of the lower leg with multiple excoriations and scaling

Ryc. 1. Przypadek 1: Rumieniowe, swędzące zmiany skórne na podudziach z licznymi przeczcosami i złuszczeniem



Fig. 2. Case 1: Erythematous skin lesions of feet with excoriations and lichenification. Fungal changes of toenails

Ryc. 2. Przypadek 1: Rumieniowe zmiany skórne na stopach z przeczcosami i liszajowaceniem. Grzybicze zmiany paznokci stóp



Fig. 3. Case 1: Distal and lateral subungual onychomycosis of the left great toenail

Ryc. 3. Przypadek 1: Dystalna i boczna podpaznokciowa grzybica paznokcia lewego palucha



Fig. 4. Case 1: Prick tests with fungal allergens 20 minutes after application - positive reaction to *Candida albicans* allergens ("C" - *C. albicans* allergens, "+" - positive control: histamine, "-" - negative control: isotonic salt solution)

Ryc. 4. Przypadek 1: Testy skórne z alergenami grzybiczymi 20 minut po aplikacji - dodatnia reakcja na alergeny *Candida albicans* („C” - alergeny *C. albicans*, „+” - kontrola dodatnia z histaminą, „-” kontrola ujemna z solą fizjologiczną)



Fig. 5. Case 2: Erythematous, itchy skin lesions of the lower leg with fissures, excoriations and fine scaling

Ryc. 5. Przypadek 2: Rumieniowe, swędzące zmiany skórne na podudziach z pęknięciami, przeczcosami i delikatnym złuszczeniem



Fig. 6. Case 2: Distal and lateral subungual onychomycosis with distinct hyperkeratosis of the great toenails

Ryc. 6. Przypadek 2: Dystalna i boczna podpaznokciowa grzybica paznokci paluchów z nasiloną hiperkeratozą



Fig. 7. Case 2: Prick tests with fungal allergens 20 minutes after application – positive reaction to *Trichophyton mentagrophytes* and slightly positive to *Candida albicans* allergens (“Tm” – *T. mentagrophytes* allergens, “Ca” – *C. albicans* allergens, “Mm” – *Mucor mucedo* allergens, “+” – positive control: histamine, “-” – negative control: isotonic salt solution)

Ryc. 7. Przypadek 2: Testy śródkórnne z alergenami grzybiczymi 20 minut po aplikacji – dodatnia reakcja na alergen *Trichophyton mentagrophytes* i słabododatnia z alergenami *Candida albicans* („Tm” – alergen *T. mentagrophytes*, „Ca” – alergen *C. albicans*, „Mm” – alergen *Mucor mucedo*, „+” – kontrola dodatnia z histaminą, „-” kontrola ujemna z solą fizjologiczną)

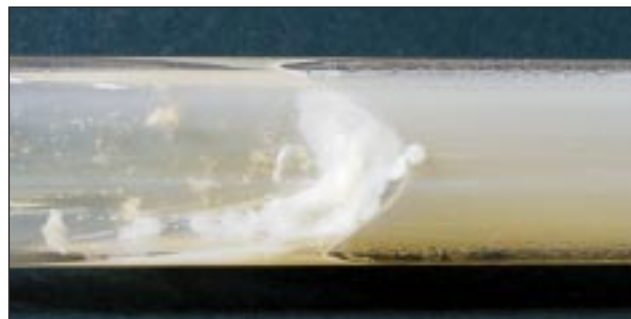


Fig. 8. Case 3: Culture of the nail specimens

Ryc. 8. Przypadek 3: Hodowla z materiału z paznokci

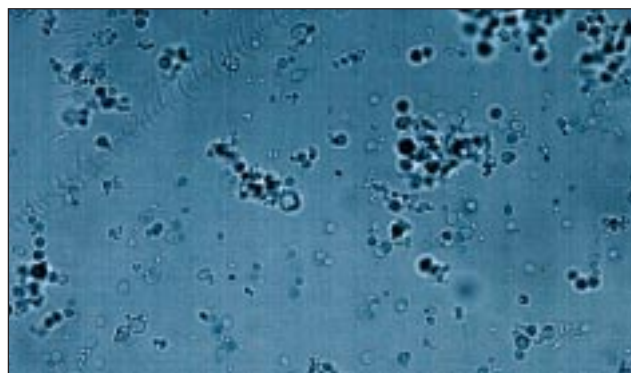


Fig. 9. Case 3: Microscopic view of the fungal culture – *Candida* sp. cells were present (original magnification 400×)

Ryc. 9. Przypadek 3: Obraz mikroskopowy hodowli grzyba – komórki *Candida* sp. (oryginalne powiększenie 400×)

bodies to *P. orbiculare* ($p < 0.0001$). These IgE antibodies were detected in 38% of the children with current eczema, in 22% of those with a history of previous eczema and only in 7% of those without eczema. Moreover, bronchial asthma and IgE-mediated food allergy were both significantly more prevalent among the children with IgE positivity to *P. orbiculare* than among those without such positive reaction ($p < 0.05$) (13). Similar results were found among AD patients with hypersensitivity to *C. albicans* allergens. All patients with severe and 77% with moderate eczema had positive *C. albicans* skin-prick tests in comparison to 39% with mild and 33% with no eczema (4). Although *C. albicans* and *P. orbiculare*/*Malassezia furfur* seemed to be a major pathogens responsible for fungal allergy, also other fungi, including dermatophytes, could play an important role in induction of allergic reactions (10, 14, 15).

Interestingly, patients presented here had no atopic history. However, all of them presented with high eosinophilia and high total serum IgE level. We may hypothesize that the reported skin lesions could be result of prolonged exposition to fungal allergens, released from nail plates. The fungal allergens, which could be present for many years in nails, could induce allergy and, as a result, could be responsible for induction and for exacerbation of eczema. It has been postulated that fungal antigens may modulate not only IgE mediated immune response, but are also able to influence others immunological pathways. Savolainen *et al.* (3) demonstrated that *Candida* sp. induced stronger rather TH_1 -associated response, activating the releasing of interleukin (IL)-2, specific IgG and IFN- γ . Opposite observations were made after exposition to *Pityrosporum* sp. allergens, which were responsible for stronger

TH_2 -like response (3). It was also observed, that *C. albicans* could activate CD69+ as well as CD25+ lymphocytes (16). Moreover, a higher proportion of patients with hypersensitivity to *Trichophyton* sp. were found among patients suffering from nonallergic asthma (63%) in comparison to patients with allergic asthma (47%) (15). Additionally, fungal allergens seemed to be also important in activation of eosinophils. It was noted that after exposition of peripheral blood mononuclear cells to *C. albicans* allergens the production of IL-5, a cytokine required for the differentiation, activation and survival of eosinophils, was significantly up-regulated (2, 3).

Based on the presented patients with eczema and literature data we do believe, that in some patients the allergic diseases could be induced or exacerbated by fungal allergens found in the nails. Therefore, it seemed reasonable to introduce anti-mycotic treatment in the group of patients, who suffer simultaneously from onychomycosis and eczema, as this treatment could be beneficial not only for fungal infection but also for allergic skin lesions.

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