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Toxic Epidermal Necrolysis and Erythema Multiforme Following Therapy with Terbinafine

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We report two cases with severe skin reactions following oral terbinafine (Lamisil®) therapy. The first case was a 49-year-old woman with onychomycosis of the toe nails. She had suffered from diabetes for 3 years, but it was well controlled on insulin. Five days after start of terbinafine 250 mg once daily she developed erythema. The treatment was continued for 2 days, but the skin eruption progressed, and a clinical diagnosis of toxic epidermal necrolysis was confirmed histologically. The second case was a 51-year-old woman with dermatomycosis on the right foot. She developed a papular eruption in the second week after taking terbinafine 250 mg once daily. Despite this eruption she continued treatment for 6 days. Generalized erythema multiforme developed in the following days. Terbinafine is a recently introduced efficacious fungicidal drug. This is the first report of toxic epidermal necrolysis following terbinafine. ***Key words: onychomycosis; skin reaction.***

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Terbinafine (Lamisil®) is a recently introduced fungicidal drug of the allylamine class with promising potential activity against a broad spectrum of fungi. Clinical trials have shown that oral terbinafine is particularly efficacious in the treatment of onychomycosis, with high cure rates (1, 2).

Terbinafine has been well tolerated at the recommended dosage of 250 mg/day with only minor adverse events such as mild to moderate gastrointestinal discomfort and skin reactions (1–4). Villars & Jones (1) reported rashes and urticaria in 1.8% of 1440 patients receiving terbinafine (250 mg/day). No severe skin reactions were seen.

Terbinafine was marketed in Denmark in October 1991, and within the first year we have seen two referred cases with severe skin reactions after treatment with oral terbinafine.

CASE REPORTS

Case 1

A 49-year-old woman with type 1 diabetes mellitus since 1989 had a 4-week history of nail changes in several toe nails. The patient had no past history of allergy or skin diseases. Insulin was the only concomitant medication.

A dermatologist diagnosed onychomycosis (*T. rubrum*) through microscopy and culture. Oral terbinafine 250 mg once daily was initiated. After 5 days the patient developed itching and a confluent maculopapular erythema on the trunk. The treatment with terbinafine was continued for 2 days, and the erythema spread to involve the extremities and the face. Treatment with topical steroid and oral antihistamine was started, but the skin eruption continued to progress with generalized peeling, oedema and large flaccid bullae of the legs. The mucosal surface was not affected. The patient was referred to our department after 4 days. The day before admission oral prednisone 25 mg/day was initiated.

We found TEN-like changes with severe peeling of epidermis in the crural areas and with a positive Nickolsky sign. The remaining part of the body had strong redness and slight scaling but was without a positive Nickolsky sign. Treatment with prednisone and topical potent steroid was continued. The severely denuded areas of the legs were dressed with silver nitrate. No intravenous fluid was necessary. The histopathologic examination of a biopsy from the lower leg established the diagnosis of toxic epidermal necrolysis (Fig. 1).

After 6 days the eruption began to clear. Re-epithelialization of the previously sloughed areas took place and the general condition remained well. The patient was discharged after 18 days.

Five blood cultures, two culture swabs from throat, one urine culture and four skin cultures were all negative. One skin culture from the leg showed hemolytic group B streptococci and treatment with penicillin G 1 million units twice daily was given for 10 days.

Slight leukocytosis (14,6 × 10–9/1) was seen with 91% granulocytes at the day of admittance, with an ensuing normalization.

ESR, haemoglobin, thrombocytes, serum creatinine, sodium, potassium, liver parameters and urine microscopy were within normal limits.

Case 2

A 51-year-old woman had had toe nail changes and suspected tinea pedis for more than 6 months. She had a history of nickel allergy, but no other skin diseases. She suffered from chronic back-aches following a disc protrusion 8 years earlier and took acetyl-salicylic, codeine and diazepame.

Two months after developing toe nail changes and suspected tinea pedis on the right foot, the patient developed eczema with blisters on the hands. A dermatologist performed several direct microscopies, which were, however, negative for fungus. Treatment with topical steroid (Betnovate) and later Bucky radiation had effect. Three months later the eczema relapsed on the fingers and the toes on the right foot, and treatment with topical steroid and Bucky radiation was repeated. One month later dermatomycosis on the right third toe was diagnosed through direct microscopy. Treatment with oral terbinafine 250 mg/day and topical Mycofen® was initiated. Two weeks after start of terbinafine the patient developed a papular eruption with blisters on the extremities. Six days later terbinafine was stopped and due to progression of the

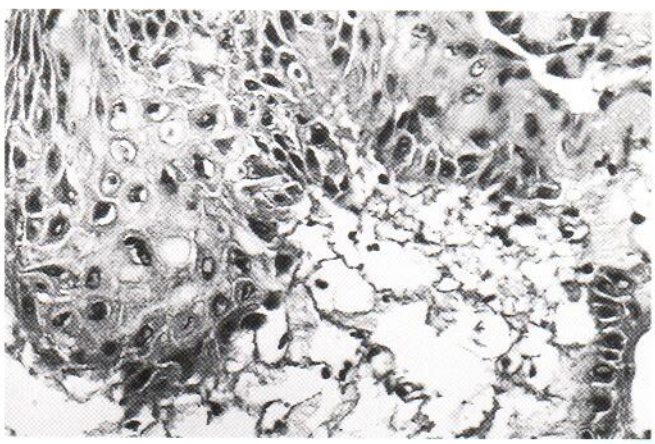

Fig. 1. Necrolytic changes in the basal keratinocytes. (Paraffin section after freezing. H & E ×325.)

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erythema, treatment with prednisone 50 mg/day and topical steroid (Dermovate®) was started. Five days later the patient was referred to our out-patient department with a severe generalized erythema multiforme. No mucous membrane involvement was observed. The clinical diagnosis was histologically confirmed, showing perivascular lymphocytic infiltration in the dermis and several degenerated keratinocytes especially in str. basale. Immunofluorescence studies were negative. The findings were compatible with the clinical diagnosis. We continued treatment with prednisone and topical steroid. At the follow-up examination one week later the erythema had faded, and one month later no permanent sequelae were noted.

ESR, haemoglobin, thrombocytes, leukocytes, creatinine, potassium, sodium and liver parameters were all within normal limits.

Epicutaneous patch tests were carried out with terbinafine 1% and placebo cream in both patients 2 months after recovery. No delayed hypersensitivity reactions were elicited. In a 4-month period we tested 147 consecutive patients with different histories of allergies and skin diseases with patch tests, including terbinafine 1% and placebo cream without demonstrating hypersensitivity or irritant reactions.

DISCUSSION

Our two patients had exhibited clinical and histological features of toxic epidermal necrolysis and erythema multiforme. These severe skin reactions were most likely induced by terbinafine.

This is the first published case of toxic epidermal necrolysis following terbinafine administration. The points implicating terbinafine are the absence of any other illness or medication except diabetes mellitus and insulin before drug administration and the time interval between start of terbinafine and the onset of the eruption. Moreover, staphylococcal scalded skin syndrome was ruled out by the histological examination and negative cultures.

In the second case it seems probable that terbinafine caused the severe skin reaction with erythema multiforme. The patient had not taken any prior medication except pain-killers. Neither of these drugs is considered to be a likely cause, because each had been taken for several years prior to the appearance of the rash, and they were continued after the rash appeared. The eczema with blisters on hands and feet early in the history was probably an "id-reaction". But the eruption on the extremities in the second week after start of terbinafine and the subsequent development of erythema multiforme after the continued treatment with terbinafine implicate that terbinafine caused the severe skin reaction.

Oral terbinafine therapy has been very well tolerated in several clinical trials, with only minor adverse effects reported (1, 2). However, our two cases stress that severe skin reactions can develop following terbinafine administration in recommended dosages.

In conclusion, it is recommended to stop treatment with terbinafine immediately if a rash develops, and before treatment it is important to inform the patient about the possible adverse effects of terbinafine.

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