

than systemic corticosteroids, especially in patients who need prolonged systemic treatment. The drug may be particularly valuable in patients who cannot be given systemic corticosteroids for some reason or other. However double-blind, controlled trials in a larger number of patients are required to establish the efficacy and safety of this drug in these patients.

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## Possible Role of Diltiazem in a Recalcitrant Case of Darier's Disease

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Sir,

The gene defect of the genodermatosis Darier's disease (DD), dyskeratosis follicularis, has been identified as the locus for sarco-endoplasmic reticulum calcium ATPase type 2 (SERCA 2) (1). The exact mechanism by which this gene abnormality leads to dyskeratosis still needs elucidation. We present a case where the calcium channel blocker diltiazem may have played a part in a complicated and severe attack of DD.

### CASE REPORT

A 51-year-old woman had suffered from severe DD since 3 years of age appearing first as filiform keratoses and pits on her palms and soles. Apart from a single admission to the hospital in 1989, when she was 38 years old, when the disease had temporarily deteriorated, she was under reasonable control as an outpatient. From 1989 intermittent episodes with superinfections caused by the herpes simplex virus, *Staphylococcus aureus* and hemolytic streptococci complicated the course of the disease. In 1991 she underwent percutaneous transluminal coronary angioplasty (PTCA) and was subsequently prescribed diltiazem (Cardil™) at 120 mg b.i.d. for ischemic heart disease. During the next few years her skin deteriorated, necessitating several yearly admissions. Our patient was convinced that the PTCA had caused the substantial worsening of her disease. In March 1999 she was admitted to hospital because of further exacerbation. The skin was universally

covered with greasy crusted papules, especially on the scalp, ears, neck, back and flexural areas. Large erythematous, erosive and fissuring areas were present on the lower back, gluteal regions, lateral aspects of the thighs and pretibial areas (Fig. 1). Bacterial colonization and infections varying between *S. aureus*, *Pseudomonas auruginosa* and hemolytic streptococci complicated the condition. Episodes of septicemia occurred. Her general state of health was weakened with anemia and depletion of zinc and protein.

Neotigason was initiated in 1989 in dosages of 25 to 50 mg daily. This treatment was stopped in June 1999 but reintroduced in August 1999. From 1989 acyclovir had been given intermittently and from 1994 continuously as a prophylactic. Antibacterial therapy was given when indicated according to bacteriology. Cyclosporine was tried for one month at 200 mg/day in 1998 and for one month in May 1999 at 400 mg/day without any response.

In early July 1999 the diltiazem treatment was stopped and one week later replaced with isosorbid-dinitrate, owing to recurrence of ischemic heart symptoms.

Estrogen/gestagen hormone replacement therapy with tibolon was given for 4 weeks but discontinued because of an increase in liver enzymes. Additional treatment included vitamins, oral zinc, iron and a protein-rich diet.

For topical treatment, medical soap and neutral moisturizing and/or dry skin products such as steroids were tried and were either not tolerated or ineffective. From the middle of July, zinc paste was applied to all moist areas, with immediate relief.



Fig. 1. Erosive Darier's disease in a 51-year-old woman.

The patient was dismissed from the hospital a month later. The skin was without erosions but with slow relapse of keratotic elements of the palms and soles (Fig. 2).



Fig. 2. Same patient 2 months after cessation of diltiazem and neotigason therapy.

## DISCUSSION

Darier's disease is an autosomal-dominant genodermatosis and the gene locus has been located to chromosome 12q23-24.1 encoding for SERCA 2 (1). It has been suggested that SERCA 2 plays a critical part in calcium-mediated control of the cell cycle (2). A co-ordinated regulation of the genes for calcium channels in the plasmalemma and in the sarcolemma has been demonstrated and the regulation in itself may be mediated by calcium ions (3). Furthermore, the calcium antagonist verapamil has been shown to influence calcium metabolism (4). SERCA 2 has been suggested to play a part in calcium-mediated keratinocyte cell-to-cell adhesion. Kitamura et al. (5) reported 15 cases of skin eruptions after treatment with diltiazem, 7 of which were psoriasiform eruptions. Exfoliative dermatitis has also been described after the use of diltiazem (6, 7).

The concurrence between the introduction of diltiazem and the gradual worsening of our patient's condition and between the substantial clinical improvements after cessation of this drug indicates a causal relation.

Neotigason was given continuously for 10 years. As this drug is known to increase skin fragility, it may have contributed to the erosive state. Reintroduction of Neotigason 2 months later, however, caused no undesirable side effects.

Oral contraceptives may be of value in the treatment of DD (8) and our patient actually had this experience when she was still menstruating. The menopause started in 1997, and after appropriate gynecological examination, the patient started hormone replacement therapy with tibolon. However, the short duration of this treatment allows no relevant evaluation of a possible effect on her skin. Cyclosporine has been used for eczematized cases of DD (9) but without any effect on erosions and papules. This observation was confirmed in our patient. Antibiotics were given according to bacteriological findings and were able to clear the skin of bacteria but without signs of healing. Topically, a third generation retinoid, tazarotene (10), was tried on one leg, the contralateral serving as control, but no effect was observed. The introduction of simple petrolatum (Vaseline®) with 10% zinc oxide gave the patient relief and may be considered as a drying and protective supplementary treatment.

A diltiazem provocation test would have excluded the natural course of the disease as background for the marked improvement but this could not be obtained. Although the exact mechanism remains obscure, diltiazem acts on the same axis as the gene defect of DD suggesting that alternative treatment modalities for ischemic heart disease in DD patients should be considered in recalcitrant cases.

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## Tinea Cruris due to Combined Infections of *Trichophyton mentagrophytes* and *Microsporum canis*. A Case Report

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Sir,

Superficial fungal infections are usually caused by a single pathogen. Mixed infections with more than one fungus are possible in a small proportion of patients. However, mixed infections due to different dermatophyte species are rare. We present here a case of tinea cruris caused by mixed infections of *Trichophyton (T.) mentagrophytes* and *Microsporum (M.) canis* in an otherwise healthy man.

### CASE REPORT

A 66-year-old man presented with a 5-month history of tinea cruris. Physical examination revealed round, marginate, erythematous scaling patches on the buttocks and groin. He had no history of animal contact or other underlying disease. Direct mycologic examination of skin scrapes in 20% KOH showed a large number of branching hyphae of regular width. Cultures in Sabouraud dextrose agar showed growths of two dermatophytes, *M. canis* and *T. mentagrophytes* var. *mentagrophytes*. Culture in potato dextrose agar with chloramphenicol with or without cycloheximide showed growths of *T. mentagrophytes* and *M. canis*. The patient was treated with isoconazole cream for 2 weeks and showed clinical cure.

### DISCUSSION

The frequency of mixed infections is uncertain in onychomycosis. In one recent study, mixed infections were reported to be infrequent and comprising only about 5% of onychomycosis cases (1). The most common combination was *T. rubrum* and *Candida* species, and a single case with mixed infections of *T. mentagrophytes* and *Trichophyton* species was described in this study. Data on mixed infections are lacking in other superficial fungal infections, although infection with single fungal pathogen is likely in most cases (2). Combined

infections of different dermatophyte species seem to be an extremely rare event. An unusual infection with *T. mentagrophytes* and *M. canis* was described in a patient with AIDS (3). A few cases of mixed fungal infections have been reported in immunocompromised hosts (2, 4–6). The majority of combined infections reported have been combinations of aspergillus and candidiasis, and other forms included aspergillosis in combination with zygomycosis. The diseases showed an aggressive course with locally invasive or systemic infections.

In our case, two different dermatophytes were isolated from the localized skin lesion of an otherwise healthy patient, and the infection showed a prompt therapeutic response to conventional antifungal agents. It is suggested that mixed infections of different dermatophytes occur rarely in an immunocompetent host.

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