

Successful Treatment of Acquired Reactive Perforating Collagenosis with Doxycycline

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Sir,

Reactive perforating collagenosis belongs to the spectrum of primary perforating skin disorders with obligatory transepithelial collagen extrusion. After transepidermal passage of the collagen, lesions tend to resolve spontaneously. An even less common, usually asymptomatic, inherited form with early onset (1) has been distinguished from a sporadic acquired type in adulthood. The latter is most frequently associated with diabetes mellitus and/or kidney failure and rarely occurs in patients with other systemic disease (2). There is no gender predilection and pruritus is a widely accepted driving force (2).

CASE REPORT

In July 2001, an 87-year-old Caucasian woman was referred to our Department of Dermatology with a one-year history of scattered skin lesions which characteristically started as umbilicated papules and progressed to ulcerated plaques, primarily located on the trunk and extensor limb surfaces (Fig. 1). The lesions manifested on severely exsiccated eczematous skin and had been insufficiently controlled by topical



Fig. 1. Exulcerated, partly excoriated skin lesions of late-stage acquired reactive perforating collagenosis on the lower legs showing distinctive dark brown crusts with raised rims and the Koebner phenomenon.

corticosteroid ointments. Medical history revealed essential hypertension for decades, cardiac failure, coronary heart disease, central retinal vein occlusion and two strokes. She was in a good general condition, afebrile and on constant weight. Family history was non-contributory. Her regular medication included triamterene (50 mg/day), hydrochlorothiazide (50 mg/day), enalapril (50 mg/day), isosorbide mononitrate (100 mg/day) and acetylsalicylic acid (100 mg/day). We were able to reduce pruritus by levocetirizine (5 mg/day), topical treatment with moisturizers and low potency steroids. For chronicized lesions with adherent plugs, minor curettage was performed after softening the keratotic material with 3% tetracycline hydrochloride ointment. Scraping was tolerated without local anaesthesia and accelerated wound healing. After the introduction of oral doxycycline (100 mg/day, given for 2 weeks) the formation of new lesions subsided within 5 days. After 10 days most lesions healed, with superficial oval scars up to 8 mm in diameter. Under local treatment with 5% urea cream her skin condition remained stable during a follow-up of 5 months.

Comprehensive laboratory investigations (haematology, serum chemistry, urinalysis, faecal occult blood test) were normal on several occasions. At admission, lactate dehydrogenase was mildly elevated (233 U/l). Daily blood glucose profiles, glycosylated haemoglobin, C-peptide, thyroid function tests and serum parathormone levels were within normal limits. Serum immunoglobulins revealed no aberrations. Further serologic tests (antinuclear antibodies, antineutrophil cytoplasmic antibodies, antiphospholipid antibodies, hepatitis screen), tumour markers (beta2-microglobulin, carcinoembryonic antigen, alpha-fetoprotein, CA 19-9) and a thrombosis marker screen (protein C and S, antithrombin III, APC resistance) were negative. Chest X-ray, abdominal and lymph node ultrasonography were unremarkable.

Histology showed a sharply demarcated invagination of the epidermis with elevated edges and a central cup-shaped plug (Fig. 2). The ulcer contained perpendicularly arranged fibres identified as collagen bundles by Masson's trichrome stain. Dermal vessel walls were slightly thickened in periodic acid-Schiff stains and surrounded by a moderate infiltrate of lymphocytes, histiocytes, neutrophils and fibroblasts. Van Gieson staining for elastic fibres was negative in the transepithelial zone. Direct immunofluorescence studies (antibodies against IgG, IgA, IgM, C3, fibrin) were negative.

DISCUSSION

The patient fulfilled Favre's diagnostic criteria for acquired reactive perforating collagenosis (ARPC), i.e. (i) histopathologic findings of elimination of necrotic basophilic collagen tissue into a cup-shaped epidermal depression, (ii) clinical presentation of umbilicated papules or nodules with a central adherent keratotic plug, and (iii) onset of skin lesions after the age of 18 years (2).

There is much debate about the pathomechanisms and their chronology resulting in transepidermal

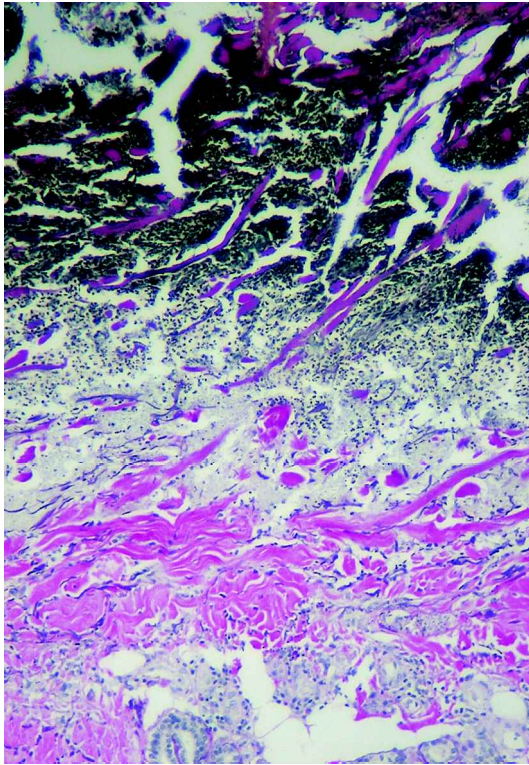


Fig. 2. Crateriform ulceration reaching to the reticular dermis and filled with nuclear debris, keratin, inflammatory cells and degenerated collagen in oblique strands indicating transepidermal elimination (van Gieson; $\times 200$).

extrusion of connective tissue. Controversy focuses on whether the basic defect in ARPC is epidermal or dermal. Pruritus with scratching has been identified as an important trigger (2, 3). Most authors state that the dermal collagen has been altered before extrusion, although ultrastructural investigations failed to detect major constitutional defects (4). Reduced blood supply due to microangiopathy and polymorphonuclear leukocytes (3, 5) are possible culprits for focal necrobiosis. However, histopathologic data on alterations of the dermal vessels in ARPC are scarce (6). The matrix-degrading activity of metalloproteinases (7) is assumed to play a decisive role in the process of transepithelial channel formation with loosening of interkeratinocyte bonds, disruption of the basement membrane and detachment of collagen fibres from the densely interwoven texture of the reticular dermis. This view is supported by experimental findings of increased levels of matrix metalloproteinases not only after epidermal injury (e.g. scratching) but also following hypoxic conditions (8) or in a diabetic state (9). These factors are pre-existent in the vast majority of patients with ARPC (2).

In our patient, xerosis aggravated by fluid depletion resulted in a generalized asteatotic dermatitis with severe pruritus, which was the main reason for admission. Treatment with emollients and antihistamines caused

considerable relief. The perforating skin lesions were treated with curettage and oral doxycycline. Spontaneous remission was unlikely in our case because the patient had a one-year clinical course without intervals of complete resolution. In view of the strong association of ARPC with diabetes mellitus or renal insufficiency, it was most unusual that our patient did not suffer from these conditions (2). However, she displayed a long history of systemic arteriopathy with elevated blood pressure, chronic heart failure, angina, retinopathy and two strokes. We believe that chronic hypertension with subsequent tissue hypoxia, upregulation of matrix metalloproteinases and superficial epidermal damage by scratching constituted pathologic factors for ARPC in our patient.

Numerous therapeutic regimens have been reported for ARPC (2, 10). As a new therapeutic approach, semisynthetic tetracycline analogues have been shown to exert various immunomodulating or antiinflammatory actions and to be potent inhibitors of matrix metalloproteinases in contrast to the parent compound, tetracycline hydrochloride (11). Recent studies have shown that tetracycline derivatives inhibit interstitial collagen loss in animal models of diabetes. By this and other mechanisms they are believed to positively influence various complications, including kidney disease, ocular lesions, osteoporosis, periodontitis and impaired wound healing (9).

We therefore suggest that the combination of antipruritic and keratolytic treatment with oral tetracycline derivatives can be an effective treatment for ARPC.

REFERENCES

1. Mehregan AH, Schwartz OD, Livingood CS. Reactive perforating collagenosis. *Arch Dermatol* 1967; 96: 277–282.
2. Faver IR, Daoud MS, Su WP. Acquired reactive perforating collagenosis. *J Am Acad Dermatol* 1994; 30: 575–580.
3. Theile-Oche S, Schneider LA, Reinhold K, Hunzelmann N, Krieg T, Scharffetter-Kochanek K. Acquired perforating collagenosis: is it due to damage by scratching? *Br J Dermatol* 2001; 145: 173–174.
4. Yanagihara M, Fujita T, Shirasaki A, Ishiguro K, Kawahara K, Ueda K. The pathogenesis of the transepithelial elimination of the collagen bundles in acquired reactive perforating collagenosis. *J Cutan Pathol* 1996; 23: 398–403.
5. Zelger B, Hintner H, Aubock J, Fritsch PO. Acquired perforating dermatosis. Transepidermal elimination of DNA material and possible role of leukocytes in pathogenesis. *Arch Dermatol* 1991; 127: 695–700.
6. Kawakami T, Saito R. Acquired reactive perforating collagenosis associated with diabetes mellitus: eight cases that meet Favre's criteria. *Br J Dermatol* 1999; 140: 521–524.
7. Briggaman RA, Schechter NM, Fraki J, Lazarus GS. Degradation of the epidermal-dermal junction by proteolytic enzymes from human skin and human polymorphonuclear leukocytes. *J Exp Med* 1984; 160: 1027–1042.
8. Yamanaka M, Ishikawa O. Hypoxic conditions decrease the mRNA expression of pro α 1(I) and (III) collagens

- and increase matrix metalloproteinases-1 of dermal fibroblasts in three-dimensional cultures. *J Dermatol Sci* 2000; 24: 99–104.
9. Ryan ME, Usman A, Ramamurthy NS, Golub LM, Greenwald RA. Excessive matrix metalloproteinase activity in diabetes: inhibition by tetracycline analogues with zinc reactivity. *Curr Med Chem* 2001; 8: 305–316.
 10. Farrell AM. Acquired perforating dermatosis in renal and diabetic patients. *Lancet* 1997; 349: 895–896.
 11. Golub LM, Ramamurthy NS, McNamara TF, Greenwald RA, Rifkin BR. Tetracyclines inhibit connective tissue breakdown: new therapeutic implications for an old family of drugs. *Crit Rev Oral Biol Med* 1991; 2: 297–321.

Erythema Multiforme-like Rash in a Patient Sensitive to Ofloxacin

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Sir,

Ofloxacin is a widely used fluorinated quinolone antibiotic that is highly active against a wide spectrum of bacteria. The most commonly described adverse effects with ofloxacin are gastrointestinal disturbances, central nervous system reactions and skin reactions (1). Among cutaneous adverse drug reactions, ofloxacin has been reported as causing fixed drug eruption (2), toxic pustuloderma (3) and hypersensitivity vasculitis (4), but no systemic contact dermatitis. We report here a case of erythema multiforme-like rash in a patient with delayed hypersensitivity to ofloxacin.

CASE REPORT

A 27-year-old man with a personal history of atopy, using topical ofloxacin (Exocin® eye-drops 0.3%) for bacterial conjunctivitis, developed acute eyelid dermatitis associated with hyperaemia and conjunctival chemosis. His lesions improved rapidly with topical corticosteroids and avoidance of the ophthalmic preparation he had used in the past. Four months later, he contracted an infection of the urinary tract and was treated with oral ofloxacin 400 mg/day (Oflocin®). Several hours after taking 200 mg of ofloxacin on the first day of treatment, the patient presented erythema, oedema and exudation of both eyelids and zygomatic regions. Nevertheless, he showed a generalized pruritic maculopapular skin rash, which was successfully treated with steroids and antihistamines.

Two months later, after giving informed consent, the patient was subjected to allergologic *in vivo* tests. Prick tests and intradermal tests with ofloxacin (at 1 and 5 mg/ml in saline) were performed without eliciting any immediate reaction. Twenty-four hours later, the patient exhibited erythema, infiltration and vesicles in the area of the intradermal test. In the zone of the prick test with ofloxacin a papulo-erythematous lesion appeared at 36 h. Subsequently, patch tests were performed with the SIDAPA standard series (Chemotecnique Diagnostics AB, Sweden), Exocin® eye-drops (as is) and

its active ingredients, including ofloxacin (5% and 25% pet.) and benzalkonium chloride (0.1% aq.). The patch preparations were applied with Finn Chambers on Scanpor following the International Contact Dermatitis Research Group recommendations. Patch tests were positive at days 2 and 4 for Exocin® as is (+ + +/+ + +), ofloxacin 5% (+/+) and ofloxacin 25% (+ + /+ + +). Prick, intradermal and patch tests with ofloxacin were negative in 15 controls.

The patient was also subjected to a single-blind placebo (talc) and to a controlled peroral challenge test with ofloxacin at gradually increasing doses, reaching a maximal dose of 200 mg. On the first day, 2 placebo capsules were administered, one every 2 h; after 7 days the patient received divided doses of ofloxacin: 50 mg initially and 150 mg 2 h later. The patient developed an erythema multiforme-like rash, localized particularly on the face, about 10 h after the administration of a total dose of 200 mg of ofloxacin. He was successfully treated with systemic corticosteroids and antihistamines.

DISCUSSION

This is the first time that oral administration of ofloxacin is reported to have caused an erythema multiforme-like rash, as a form of systemic contact dermatitis, in a patient with delayed contact hypersensitivity to this drug. Systemic contact dermatitis can appear only in previously contact sensitized subjects when the allergen is introduced systemically (5) and it shows itself with skin signs and often with systemic signs. Skin signs can be various types of reaction: relapse or aggravation of the primitive contact dermatitis or, more rarely, generalized various morphology eruptions. Our patient developed an erythema multiforme-like rash that, unlike classic erythema multiforme, presents neither evident bullous lesions nor mucous membrane involvement.

Allergens responsible for systemic contact dermatitis are especially drugs, but also metals, food additives, formaldehyde and mercury. Although few experimental data are present in the literature, it has been suggested