7. Mancini RE, Quaife JV. Histogenesis of experimentally produced keloids. J Invest Dermatol 1962; 38: 143–181.
8. Renfro L, Miller D, Raszi L, Kamino H. Persistent plaque on the shoulder of a Chinese woman. BCG granuloma. Arch Dermatol 1993; 129: 231–236.
9. Misery L, Combemale P. BCG-vaccine-induced lupus vulgaris and urticarial vasculitis. Dermatology 1993; 186: 274.
10. Shea CR, Imber MJ, Cropely TG, Cosimi AB, Sober AJ. Granulomatous eruption after BCG vaccine immunotherapy for malignant melanoma. J Am Acad Dermatol 1989; 21: 1119–1122.
11. Jaffrey IS. Systemic epithelioid granulomata following immunotherapy with methanol extracted residue of bacillus Calmette-Guérin. Cancer Treat Rep 1978; 62: 573.
12. Rosenberg SA, Seipp C, Sears HF. Clinical and immunologic studies of disseminated BCG infection. Cancer 1978; 41: 1771–1780.
13. Magnon R, DeVillez RL. Disseminated cutaneous granulomas from BCG therapy. Arch Dermatol 1980; 116: 355.
14. Kuniyuki S, Asada M. An ulcerated lesion at the BCG vaccination site during the course of Kawasaki disease. J Am Acad Dermatol 1997; 37: 303–304.
15. Yokota S, Tsubaki K, Kuriyama T, Shimizu H, Ibe M, Mitsuda T, et al. Presence in Kawasaki disease of antibodies to mycobacterial heatshock protein HSP65 and autoantibodies to epitopes of human HSP65 cognate antigen. Clin Immunol Immunopathol 1993; 67: 163–170.
16. Park YM, Kang H, Cho SH, Cho BK. Lichen scrofulosorum-like eruption localized to multipuncture BCG vaccination site. J Am Acad Dermatol 1999: 41: 262–264.

Ketoprofen-induced Pemphigus-like Dermatosis: Localized Contact Pemphigus?

Jean Kanitakis, Anne-Laure Souillet, Michel Faure and Alain Claudy
Department of Dermatology, Hôp. Ed. Herriot (Pav. R), FR-69437 Lyon Cédex 03, France. E-mail: kanitak@lyon151.inserm.fr
Accepted April 10, 2001.

Sir,

Ketoprofen is a non-steroidal anti-inflammatory drug, belonging to the group of arylpropionic derivatives, which is widely used per os and by cutaneous application as a 2.5% gel. Side-effects after oral administration mainly relate to the gastrointestinal tract and affect up to 15.3% of patients (1). Cutaneous side-effects secondary to local application are much rarer, with an estimated frequency ranging from 0.008% to 0.023% (2), depending on the commercial preparation. These consist mainly of contact dermatitis (3–6) and photocontact dermatitis (7–9), which may be persistent (10). We present herein a patient who developed a vesiculobullous dermatosis at the site of application of ketoprofen, with histologic and immunopathologic features of autoimmune pemphigus. As far as we know, contact pemphigus has never been reported before with ketoprofen.

CASE REPORT

A 65-year-old Caucasian woman had been suffering from Waldenström's macroglobulinemia and was treated with fludarabin. Some days prior to consultation she had applied ketoprofen gel (Ketum) on her knees on two occasions to relieve arthralgia. Within a matter of hours she developed pruritic, well-demarcated, erythematous lesions over both knees, which later became studded with vesicles and small bullae (Fig. 1). On examination an additional erythematous lesion was found on the thigh. The mucous membranes were unaffected. The vesicles and bullae subsided as a result of local steroid treatment but the erythema persisted on the knees for the next 10 days. Histologic examination of a skin lesion showed a moderately acanthotic epidermis. Several deeply-seated intraepidermal vesicles were found, whose floor consisted of a single row of basal keratinocytes. The vesicles were occasionally coalescing into small blisters and contained many eosinophils (Fig. 2). The underlying dermis contained a mild inflammatory infiltrate composed of lymphocytes and eosinophils. Direct immunofluorescence performed twice on perilesional skin (at the initial consultation and 10 days later) showed deposits of IgG and C3 on the surface of epidermal keratinocytes, i.e. an aspect of autoimmune pemphigus.

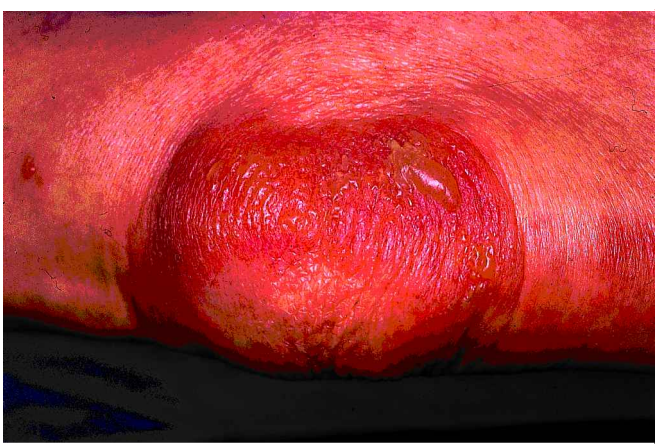

Fig. 1. Well-demarcated erythematous lesion of the knee studded with vesicles and small bullae.

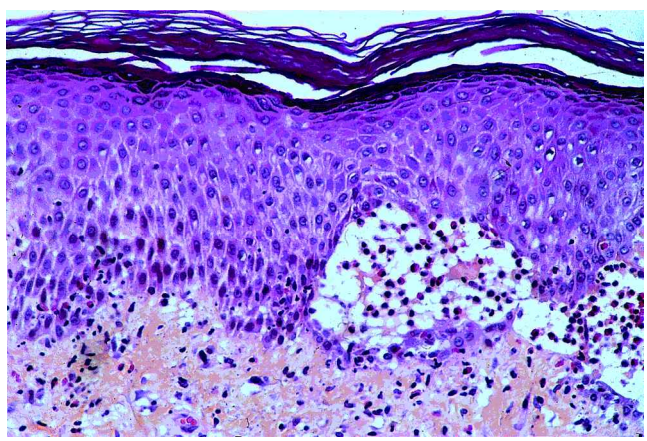

Fig. 2. Suprabasal intraepidermal clefting containing many eosinophils. Original magnification ×250.

Indirect immunofluorescence performed on two epithelial substrates (monkey esophagus and rabbit lip) and immunoblotting were negative. The patient was lost to follow-up and patch tests could not be performed.

DISCUSSION

Pemphigus encompasses a group of autoimmune diseases showing histologic intraepidermal clefting due to acantholysis, and immunopathologically tissue-bound autoantibodies to desmosomal antigens of keratinocytes, involved in cell–cell adhesion. The precise cause of the disease is unknown. Several observations suggest that at least some cases may be elicited or triggered by contact with exogenous chemicals, namely pesticides or chromium sulfate (11–13). This subgroup, referred to as "contact pemphigus", often starts as contact dermatitis before evolving into overt pemphigus. Although the majority of contact pemphigus cases present with diffuse lesions, these may occasionally remain localized at the site of contact with the responsible chemical (14). The mechanism of bulla development in contact pemphigus is not well known. It has been speculated that the applied chemicals activate endogenous enzymes that in turn induce keratinocyte disaggregation, without the intervention of an immunologic mechanism. Several anti-inflammatory drugs, including piroxicam, are able to induce acantholysis *in vitro* (15). Alternatively, contact with the responsible chemical could lead to alteration of epidermal structures, leading to the formation of neoantigens and the production of pemphigus autoantibodies. These would bind the epidermal neoantigens, localized to the area of contact with the offending molecule, explaining the fact that the lesions may be localized (14).

In our case, the clinical aspect of the lesions and the pruritus were consistent with contact dermatitis, but histology showed suprabasal clefting with formation of intraepidermal vesicles and bullae, i.e. an aspect suggestive of pemphigus. The epidermis adjacent to the vesicles was not spongiotic, as would be expected in an eczematous reaction. Remarkably, direct immunofluorescence, performed twice within a 10-day interval, showed an aspect of autoimmune pemphigus. Therefore, we believe this case to be an example of localized, contact pemphigus. The fact that indirect immunofluorescence and immunoblotting were negative does not exclude this diagnosis as circulating autoantibodies are only detected in 57% of (generalized) drug-induced pemphigus cases (16). The absence of detectable circulating autoantibodies could explain why the lesions of our patient remained localized over a limited cutaneous area. An additional factor that could account, at least in part, for the localized nature of the dermatosis in the present case is the rather low systemic absorption of ketoprofen from the knee (17).

The present report shows that ketoprofen may induce (localized) pemphigus, and raises the possibility that cases of diffuse pemphigus could theoretically be induced by this drug after application to areas showing higher absorption of the drug (such as the back and arms) (17), or after systemic administration in previously sensitized patients. We therefore believe that a meticulous history of drug usage should be taken before prescribing local or systemic ketoprofen.

REFERENCES

1. Le Loet X. Safety of ketoprofen in the elderly: a prospective study on 20000 patients. Scand J Rheumatol Suppl 1989; 83: 21–27.
2. Baudot S, Milpied B, Larousse C. Kétoprofène gel et effets secondaires cutanés: bilan d'une enquête sur 337 notifications. Therapie 1998; 53: 137–144.
3. Angelini G, Vena G. Contact allergy to ketoprofen. Contact Dermatitis 1983; 9: 234.
4. Mozzanica N, Pigato P. Contact and photocontact allergy to ketoprofen: clinical and experimental study. Contact Dermatitis 1990; 23: 336–340.
5. Tosti A, Gaddoni G, Valeri F. Contact allergy to ketoprofen: report of 7 cases. Contact Dermatitis 1990; 23: 112–113.
6. Vialsecchi R, Falgheri G, Cainelli T. Contact dermatitis to ketoprofen. Contact Dermatitis 1983; 9: 163–164.
7. Jeanmougin M, Petit A, Mangiet J, Sigal M, Dubertret L. Eczéma photoallergique de contact au kétoprofène. Ann Dermatol Venereol 1996; 123: 251–255.
8. Bastien M, Milpied-Homsi B, Baudot S, Dutartre H, Litoux P. Photosensibilisation de contact au kétoprofène. Ann Dermatol Venereol 1997; 124: 523–526.
9. Sugiura M, Hayakawa R, Kato Y, Sugiura K, Ueda H. Four cases of photocontact dermatitis due to ketoprofen. Contact Dermatitis 2000; 43: 16–19.
10. Albes B, Marguery M, Schwarze H, Journe F, Loche F, Bazex J. Prolonged photosensitivity following contact photoallergy to ketoprofen. Dermatology 2000; 201: 171–174.
11. Brenner S, Wolf R, Ruocco V. Contact pemphigus: a subgroup of induced pemphigus. Int J Dermatol 1994; 33: 843–845.
12. Vozza A, Ruocco V, Brenner S, Wolf R. Contact pemphigus. Int J Dermatol 1996; 35: 199–201.
13. Tsankov N, Kazantchieva J, Gantcheva M. Contact pemphigus induced by dihydrodiphenyltrichlorethane. Eur J Dermatol 1998; 8: 442–443.
14. Stransky L. Contact pemphigus vulgaris? Contact Dermatitis 1998; 38: 45.
15. De Dobbeeller G, Godfrine S, Gordain JM, De Graef C, Heenen M. In vitro acantholysis induced by D-penicillamine, captopril, and piroxicam on dead re-epidermized dermis. J Cutan Pathol 1992; 19: 181–186.
16. Brenner S, Bialy-Golan A, Ruocco V. Drug-induced pemphigus. In: Kanitakis J, Vassileva S, Woodley D, eds. Diagnostic immunohistochemistry of the skin. An illustrated text. London: Chapman & Hall, 1998: 84–94.
17. Shah A, Wei G, Lanman R, Bhargava V, Weir S. Percutaneous absorption of ketoprofen from different anatomical sites in man. Pharm Res 1996; 13: 168–172.