

Drug-triggered Pemphigus in a Predisposed Woman

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A 31-year-old woman with three pemphigus-prone antigens in her HLA haplotype (B7, DR4, DQw7) developed the disease soon after taking a pyrazolone derivative, viz. feprazone. The pemphigus lesions persisted despite withdrawal of the drug and worsened appreciably when she used ceftriaxone (a new cephalosporin with three sulphur atoms) for a bout of acute pharyngitis. Thiol groups formed from the metabolic breakdown of ceftriaxone are thought to have promoted acantholysis via a biochemical route. Genetic predisposition alone ('the soil') may be essential, though not *per se* sufficient for outbreak of pemphigus; the intervention of exogenous, heterogeneous factors ('the seed') often seems decisive in triggering full-blown disease. Key words: Pemphigus (genetic susceptibility to; Provoking factors).

(Accepted June 15, 1991.)

Acta Derm Venereol (Stockh) 1992; 72: 48–49.

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The cause of pemphigus is still unknown. However, in recent years, three important aspects of this topic have been elucidated: (a) genetic factors are involved in disease susceptibility (1); (b) the disease often seems to be induced by various triggering factors such as drugs (mainly thiol drugs), physical agents, viruses, neoplasms, etc. (2,3); (c) pemphigus vulgaris and pemphigus foliaceus antigens both form disulfide bonds

with a protein of adherent junctions and desmosomes (placoglobin) (4).

This may explain why in predisposed subjects the onset of pemphigus is often facilitated by the administration of drugs that have thiol groups in their molecule (e.g. penicillamine, captopril, thiopronine) or in the molecules of their metabolites (e.g. piroxicam, some pyrazolone derivatives, and some cephalosporins). The following clinical case illustrates this concept.

CASE REPORT

Clinical history

A 31-year-old woman, with no previous history of oral or skin disease, was prescribed feprazone (Zepelin[®], De Angeli), 600 mg daily, for a painful dysodontiasis of the third molar. After a few days of treatment she complained of tongue burning and developed two small erosions at the tip and the edge of the tongue. Once feprazone was withdrawn, the erosions and burning sensation both disappeared within a week.

One month later, the patient experienced a severe backache and decided on her own to treat it with feprazone. After she had taken two doses of the drug, she had to discontinue because of sudden onset of nausea. The next day, painful erosions appeared on the labial, buccal, and retromolar mucosa; the lesions persisted for 2 months without healing. Then the patient suffered an acute bout of pharyngitis, with fever, malaise, and swollen submandibular lymph nodes, for which she was prescribed ceftriaxone (Rocefin[®], Roche), 1 g i.m. daily for a week. Following this treatment, the oral erosions worsened: there was

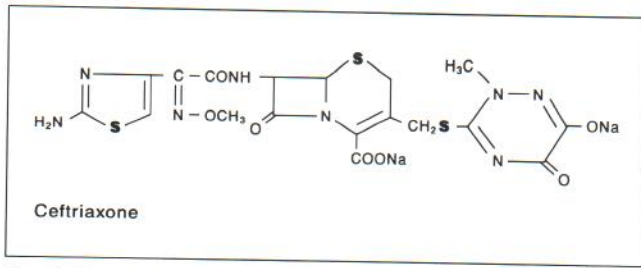


Fig. 1. Structural formula of ceftriaxone: three sulphur atoms are present in the molecule.

also a tongue and palate involvement; moreover, two flaccid bullae appeared, one in an axilla, the other in the umbilicus.

Laboratory investigations

Tzanck test on a buccal erosion showed acantholytic cells. Histologic examination of the axillary bulla revealed an intra-epidermal suprabasilar cleavage. Direct immunofluorescence studies disclosed pericellular deposits of IgG on cytological smears from the buccal mucosa and intercellular deposits of IgG and C3 on the perilesional epidermis of the biopsy specimen. Indirect immunofluorescence demonstrated an anti-intercellular substance antibody titre of 1:80. HLA typing displayed the following haplotype: A23, 29; B7, -; Cw7, -; DR4, w11, w52, w53; DQw7, -.

The diagnosis of pemphigus vulgaris was made and a conventional treatment with deflazacort (120 mg/day) started.

DISCUSSION

According to previously published criteria (2), our case features a typical example of drug-triggered pemphigus in an individual with a genetic predisposition to the disease. The pemphigus-prone background is revealed by three HLA antigens found in the patient's haplotype: B7, which raises the relative risk to 4.37 (5); DR4, a well-known genetic marker of the disease (6); and DQw7, the main subgroup of DQw3 (7) which – nearly always associated with DR4 (1) – has been detected in pemphigus patients with a significantly high frequency (8). The clinical history clearly denotes the role of feprazone in triggering pemphigus and that of ceftriaxone in aggravating its course. Feprazone belongs to pyrazolone derivatives, a drug category that is known to be capable of inducing pemphigus (9). Ceftriaxone is a new cephalosporin, which so far has never been suspected of being a possible pemphigus exacerbating agent. However, the chemical structure of this drug (Fig. 1) contains three sulphur atoms (10), which can generate thiol groups from hydrolytic breakdown. It is now well known that thiols promote acantholysis also by a biochemical mechanism, i.e., by interfering with the disulfide bonds that secure cell-cell adhesion of the malpighian epithelia (2, 3, 9, 11).

Our case and similar ones (12, 13) show that the onset of pemphigus often depends on an interaction between endogenous, genetic factors ('the soil'), and exogenous, heterogeneous, provoking agents ('the seed'). The occurrence of the disease in only one of two monozygotic twins with an identical HLA phenotype (14) strongly supports this and clearly indicates that a genetic predisposition may be essential – though not per se sufficient – for the outbreak of pemphigus.

ACKNOWLEDGEMENTS

Dr A. Marfella informed us about the pharmacological aspects of the drugs involved and Mrs M. P. Bernardo assisted in the bibliographic research.

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