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PENICILLAMINE-INDUCED PEMPHIGUS FOLIACEUS

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Abstract. A 61-year-old man suffering from active generalized scleroderma developed pemphigus foliaceus after 9 months of D-penicillamine therapy, 900–1200 mg daily. At the same time, he developed proteinuria. Upon discontinuation of the drug, the proteinuria quickly resolved, but the bullous disease was still active one year later, with development of fresh blisters and intercellular deposits of immunoglobulin G and complement C_3. The theory is proposed that D-penicillamine alters the epidermal cement substance, rendering it antigenic and thus initiating a vicious circle.

Key words: Penicillamine side-effect; Generalized scleroderma; Pemphigus foliaceus

Penicillamine is an amino acid which occurs as a product of the hydrolysis of penicillin. It is a chelating agent with metal sequestering activity which was the basis of its introduction in 1965 as a suitable remedy for Wilson's disease and lead poisoning (14). The effect of long-term penicillamine therapy in patients suffering from rheumatoid arthritis (RA) has been investigated during the last decade and recent information demonstrates its efficacy in this condition (11). In generalized scleroderma there is evidence that increased production of collagen and glyco- and/or mucoprotein takes place (10). On the basis of the in vitro finding that penicillamine is able to impede collagen formation, it was introduced in the treatment of generalized scleroderma at this Department in 1960 (2, 3).

Various adverse effects of the drug are now recognized. The side-effects of penicillamine treatment necessitate its discontinuation in one-third of RA patients so treated (11). Wellknown side-effects are vagaries or loss of taste, thrombocytopenia, proteinuria and hæmaturia. Even immune-complex nephropathia, dermatomyositis and lupus syndrome have been described (1, 6, 7, 9, 11). Skin eruptions are frequent, in most cases harmless and yielding to withdrawal of the drug. They include local or generalized erythematous, maculopapular or urticarial reactions, pruritus, and dryness and scaling of the skin (9).

Recently, penicillamine-induced bullous disorders of the pemphigus type have been reported in patients who underwent treatment for RA (8). The present case seems to be the first case of pemphigus foliaceus developing in a patient receiving penicillamine treatment for generalized scleroderma.

CASE REPORT

A 61-year-old man was admitted to the Department because of progressive generalized scleroderma (diffuse systemic sclerosis) involving the torso and the thighs. On X-ray examination, sclerodermic changes were found in the lungs and in the oesophagus. Laboratory studies were all normal, including the ESR, serum immunoglobulins and urinalysis.

The patient was started on D-penicillamine 300 mg three times a day and was then discharged. At the routine readmission 5 months later no improvement was found and the dose of D-penicillamine was increased to 300 mg four times a day. After 9 months of penicillamine treatment the patient developed bullae, scattered over the trunk. The bullae were flaccid, fragile and rupturing, gradually developing keratotic crusts covering oozing surfaces. The sign of Nikolsky was positive (Fig. 1). The histopathological examination confirmed the clinical diagnosis of pemphigus foliaceus, showing subcorneal bullae and acantholysis (Fig. 2). Studies of the lesions revealed intercellular deposits of IgG and C_3 in the epidermis while examinations for IgA, IgM and IgE came out negative.

Simultaneous with the skin changes the patient developed proteinuria of 1 g/24 hours. D-penicillamine was discontinued, and 3 months later the proteinuria resolved. The patient still developed bullae one year after the beginning of the symptoms.

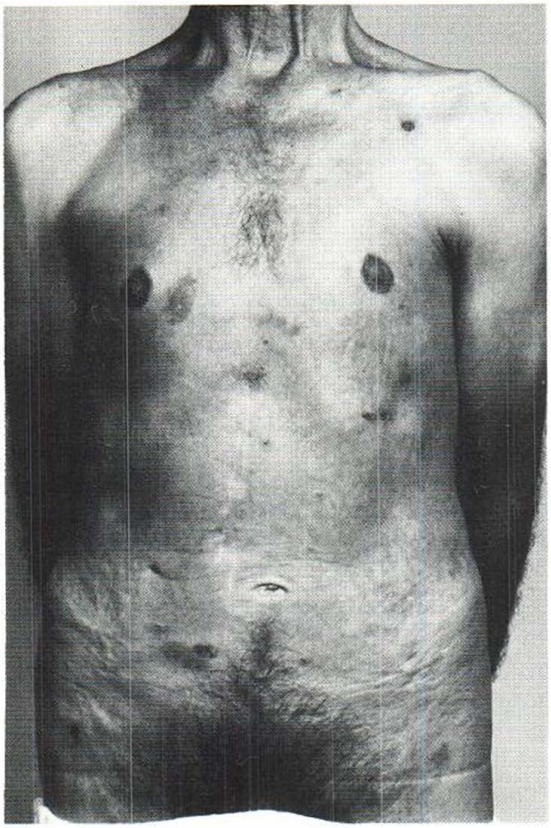

Fig. 1. Pemphigus foliaceus elements scattered on the torso of the patient. Note the sclerodermatous skin on the hips.

COMMENTS

The clinical appearance of the patient presented in this report was that of classical pemphigus foliaceus. Furthermore, histological examination of biopsy specimens revealed typical changes. The bullae appeared simultaneously with proteinuria, one of the most frequent side-effects of penicillamine treatment (9). On withdrawal of the drug the proteinuria disappeared, while the bullous disorder remained active. Recently, a preliminary report of pemphigus-like conditions developing in RA patients treated with penicillamine has been published (8). In some of these patients, the bullous disease persisted, despite discontinuation of the penicillamine treatment.

In most cases of pemphigus vulgaris and foliaceus, intercellular deposits of IgG can be demonstrated by direct and indirect immunofluorescence marking (4). Epidermal intercellular IgG antibodies have been reported in morbilliform penicillin eruptions (5), in a trichophyton rubrum infection (15), in two cases of toxic epidermolysis induced by penicillin and chlorpromazine (17), and also in burns (18). It has recently been shown that pemphigus antigens may share the structural configuration of epidermal surface proteins (12, 13, 16). From a theoretical point of view, it is possible that natural epidermal surface proteins be transformed to antigenic structures under the influence of drugs, heat, infectious agents and other unknown factors, resulting in antibody formation against these structures and in some cases initiating a vicious circle with new destruction, new antibody formation, etc.

The finding in our patient of IgG deposits in the epidermis might be explained by the formation of antigenic intercellular material under the influence of D-penicillamine. To evaluate this possibility, further studies on the adverse effects are necessary and may provide a clue to a better understanding of the pathogenetic mechanisms in the development of the pemphigous group of diseases.

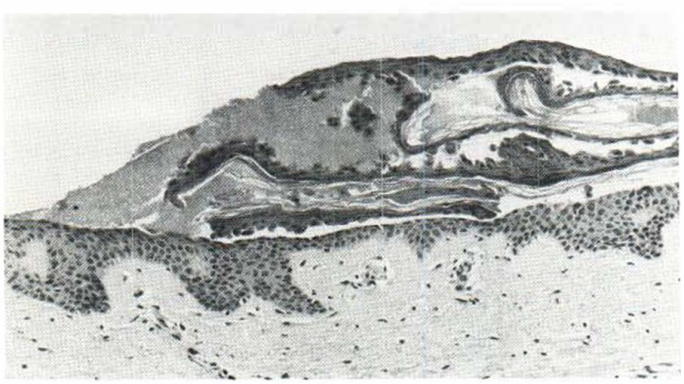

Fig. 2. A subcorneal bulla with acantholytic cells in the lumen.

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