Pemphigus foliaceus in a Haemophilic Child: Cytomegalovirus Induction?

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Abstract. A 3½-year-old haemophilic child, repeatedly transfused with blood products, developed pemphigus foliaceus with presence in serum of both intercellular and anti-cytomegalovirus antibodies at high titre. The locus A26, which seems to be a genetic marker of pemphigus, was detected in his haplotype. Cytomegalovirus infection of transfusional origin is suspected to have triggered the outbreak of pemphigus.

Key words: Pemphigus; Haemophilia; Hl.A antigens; Cytomegalovirus

Pemphigus foliaceus is an uncommon disease and rarely occurs in childhood. To the best of our knowledge its occurrence in a haemophilic child has not yet been reported. This prompted us to publish our case, which may stimulate investigation in more than one direction.

CASE REPORT

The patient, of Neapolitan extraction, aged 3 years 8 months when first seen at our clinic, was affected with haemophilia A from birth, as also was his maternal uncle. Due to bleeding traumatic wounds he had received three transfusions of antihaemophilic globulin (factor VIII) in the course of the last year. At age 3 years 6 months, during hospitalization in a Department of Haematology, he developed many groups of vesicles and small bullae, surrounded by erythema first on the scalp and trunk, afterwards on the limbs. The lesions itched mildly and quickly resulted in erosions, scaling and crusting plaques.

Based on the clinical diagnosis of bullous impetigo, a topical and systemic antibiotic treatment was started. Two weeks later, because of increased severity of the eruption despite the antibiotic therapy, the patient was transferred to our clinic.

On examination there were extensive areas of scaling, crusted lesions, and occasional flaccid bullae on the scalp, trunk (Fig. 1), and limbs. There was no involvement of the oral mucosa.

During hospitalization many laboratory investigations were carried out, and the results of the main ones are reported here.

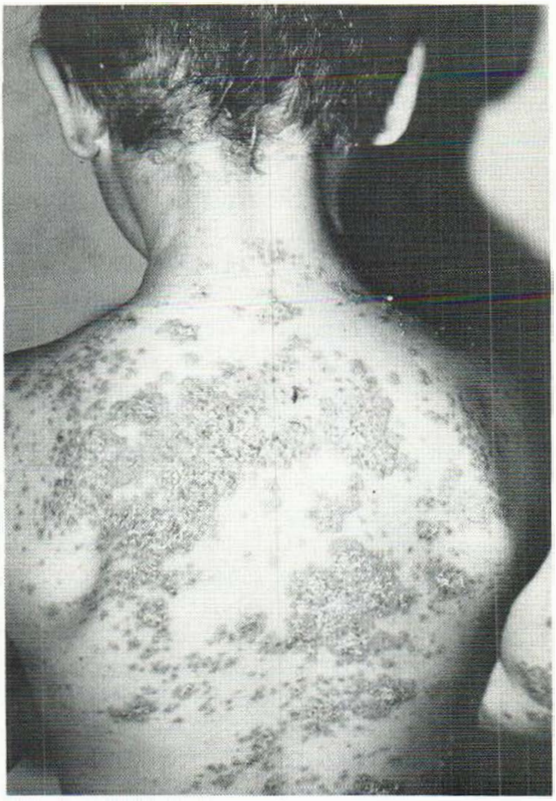

Fig. 1. Clinical picture on admission.

Haematological investigations

Blood count: RC, 4 500 000; WC, 5 600; N 39%, E 7%, L 54%; platelets, 200 000. Partial thromboplastin time: >2 min (n.v. 35–45 sec). Factor VIII level: 2% (n.v. 50–150%).

Serum immunological investigations

IgG: 1 866 mg/100 ml; IgA 124 mg/100 ml; IgM: 83 mg/100 ml. C_3: 90 mg/100 ml; C_4: 24 mg/100 ml. Tests for antinuclear factors were negative. Indirect immunofluorescence using monkey oesophagus showed intercellular deposits of IgG up to a titre of 1 : 640, but absence of any junctional deposits. Complement fixation for anti-cytomegalovirus antibodies resulted positive up to a titre of 1 : 64, (n.v. < 1 : 8).

Cyto-histological investigations

Light microscopy: The Tzanck test showed both acantholytic cells and patterns of cell adhesion, i.e. Sertoli's rosettes (8) and leukocyte adherence (6). A biopsy of an early bulla demonstrated subcorneal acantholytic splits (Fig. 2).

UV microscopy: Direct immunofluorescence on cytological smears showed deposition of IgG and C_3 with an intercellular pattern on grouped cells (Fig. 3), and a pericellular pattern on isolated cells. Direct immunofluorescence on histological sections of perilesional epi-

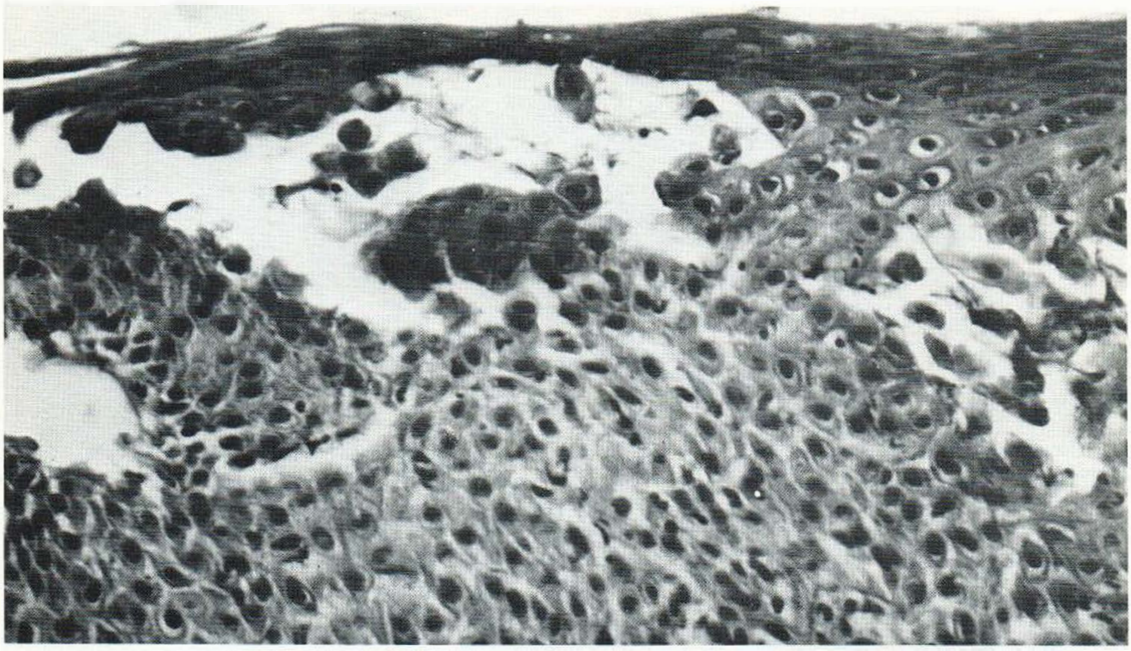

Fig. 2. Subcroneal acantholytic splits. H&E. ×250.

dermis revealed intercellular deposits of IgG and C_3, particularly in the uppermost layers; no junctional reaction was observed.

HLA typing

The patient's HLA antigens, as well as his parents', were typed, and the following haplotypes were found. Patient: Aw24-A26/Bw35-x/Cw4-y. Father: A26-A29/B7-x/y-y'. Mother: A2-Aw24/Bw35-x/Cw4-y. It was not possible to type loci D and DR.

On the basis of immunological and cyto-histological findings, a diagnosis of pemphigus foliaceus was made, and oral betamethasone therapy was started at a dosage of 4.5 mg daily. Lesions regressed completely within 4 weeks and the patient was discharged with a dosage of 4.5 mg of betamethasone every second day. Two months later clinical remission was still persistent and on repeating some immunological investigations on his serum, a significant decrease in antibody titres was found: intercellular antibodies up to 1 : 20, anti-cytomegalovirus antibodies up to 1 : 8. Steroid treatment was stopped and the patient's parents were asked to bring their son to our clinic again for monthly check-ups.

Throughout 8 months the patient remained free from lesions except for only once in the last September when a few crusted scalp plaques were observed, and soon healed by use of a steroid ointment alone; no increase in titres of either intercellular or anti-cytomegalovirus antibodies was ever detected.

DISCUSSION

This case may be regarded as an association of a classic inherited disease (haemophilia) with an autoimmune disorder (pemphigus) for which a genetic predisposition is strongly suggested by recent reports on HLA antigens (5, 7, 1).

By closely examining our patient's and his parents' HLA haplotypes an interesting observation can be made. The child inherited from his mother certain loci, namely Aw24 and Bw35, which have also been found in a series of immunologically investigated haemophiliacs (4), and from his father the locus A26 which seems to be a genetic marker of pemphigus among Japanese (3) and Jews (5, 1). It is worthwhile noting that the locus A26, moderately frequent in our region (10), is linked to the locus DRw4 (9) which seems to be the most implicated antigen in the onset of pemphigus among Jews (5). These data all support the above-mentioned assumption that the occurrence of pemphigus requires a peculiar genotype (this fact being certain regarding haemophilia), and furthermore throw new light on the possible interrelationship between genetic and immune disorders. It must be said, however, that the familial incidence and the onset in childhood are both a hallmark of haemophilia, whereas they occur only exceptionally in pemphigus. This discrepancy might be linked to the different degree of penetrance of implicated genes. In other terms, genetic factors, that are now known to play a basic role in pemphigus as well as in haemophilia, are

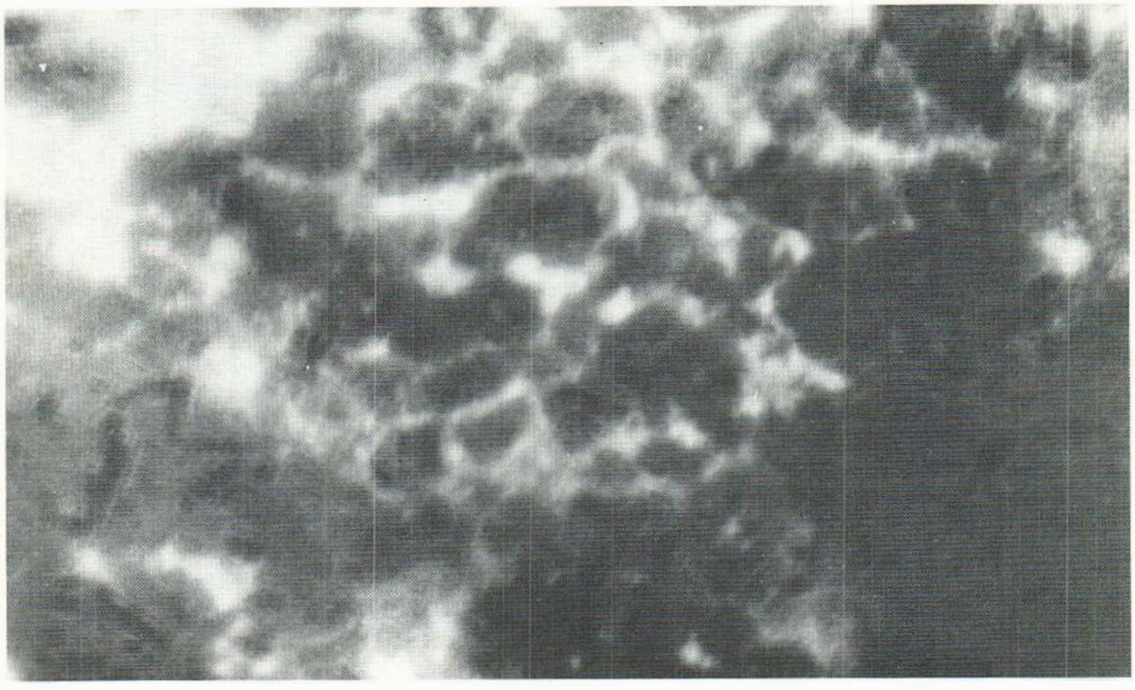

Fig. 3. Direct immunofluorescence staining on a cytological smear showing intercellular deposits of IgG. Anti-IgG serum conjugated with fluorescein. ×600.

causative for the onset of haemophilia, whereas they can only predispose to pemphigus, the outbreak of which is probably dependent on a wide variety of other factors, either endogenous (immunological defects) or exogenous (drugs, physical agents, viruses, etc.).

A virus involvement may be taken into account in our case. In fact, it can reasonably be assumed that a cytomegalovirus infection, possibly a consequence of treatment with blood products, has triggered the outbreak of pemphigus, the predisposition for which was already coded in the patient's genotype. This view is supported by three data: (*a*) the patient has A26 in his haplotype; (*b*) in the patient's serum anti-cytomegalovirus antibodies were detected, the titre of which reflected the pemphigus activity; (*c*) cytomegalovirus is known to be able to alter the host immune response, probably because it persistently infects lymphocytes and other immune cells (2).

This prompted us to search for anti-cytomegalovirus antibodies in the serum of other patients with active pemphigus. The investigation comprised 10 patients (6 with p. vulgaris, 2 with p. erythematosus, one with p. foliaceus, one with p. herpetiformis) aged from 36 to 62, all with extensive skin lesions and circulating intercellular antibodies at titres exceeding 1 : 160. No anti-cytomegalovirus antibody was detected in eight sera; in two sera antibodies were found at the titre 1 : 8, which is so low that it must be regarded as falling within the standard fixed.

Although restricted to a small number of cases, these findings do not support the possibility of pemphigus induction by cytomegalovirus as a rule, but a sporadic occurrence of such an event, as in the child presented above, still remains reasonably tenable.

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Multiple Comedones Confined to Xanthelasma

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Abstract. A case of multiple comedones which had developed on the xanthelasma of both upper eyelids of a 52-year-old woman is reported. It is suggested that there is a close relationship between comedones and xanthelasma.

Key words: Comedones; Xanthelasma

A comedo is a black or grey-brown horny plug projecting from a pilosebaceous orifice. They may arise in naevoid form, as acne vulgaris, familial comedones, acne venenata, and comedones following therapeutic irradiation, or in pseudoxanthoma elasticum and solar elastosis (1).

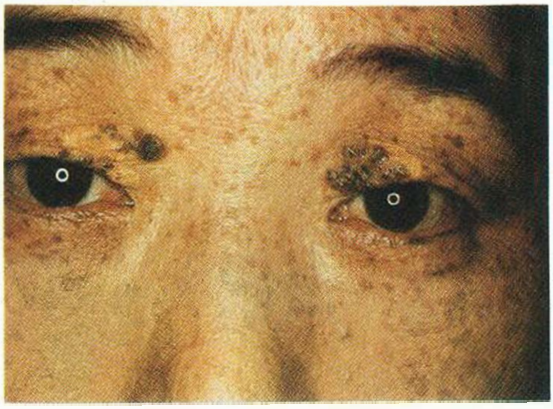

Fig. 1. Multiple comedones are seen confined to the yellowish plaques on both upper eyelids.

The comedones we present here were confined to xanthelasma and do not resemble any comedone form previously reported.

REPORT OF A CASE

A 52-year-old Japanese woman with multiple comedones on her upper eyelids was first seen in July 1981. She has had yellowish plaques on her upper eyelids for the past 5 years, on which the comedones have been developing. There was no history of acne vulgaris, UV or cobalt irradiation, excessive sun exposure, topical or systemic steroids or other therapies on the face (including the eyelids).

Results of physical examination, apart from skin lesions, were normal. She has had light-brown, pigmented macules, so-called freckles, scattered on the face since she was around 15 years old. A yellowish plaque measuring 1×3 cm was seen on the inner region of each upper eyelid (Figs. 1 and 2). There were about 20 and 10 come-

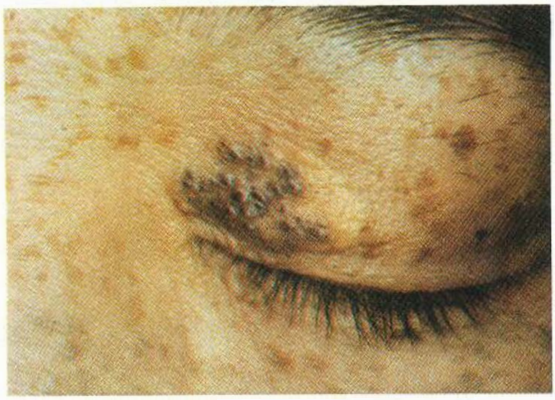

Fig. 2. Higher power view of comedones on the left upper eyelid.