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MIXED FORM OF DERMATITIS HERPETIFORMIS AND BULLOUS PEMPHIGOID

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Abstract. Two cases of bullous disease had clinical and histological features suggestive of both dermatitis herpetiformis (DH) and bullous pemphigoid (BP). Immunofluorescence (IF) studies on both diseased and healthy skin tissue revealed in the one patient an intense linear deposit of IgG and C3 along the dermo-epidermal junction and in the other patient a linear deposit of IgA and C3 along the dermo-epidermal junction. No circulating anti-basement membrane antibodies were found. At the time of investigation in both cases normal jejunal mucosa was observed. Both patients carried the HLA-DRw3 antigen, which has been found associated with DH. One of them responded to treatment with diasone-sodium combined with a gluten-free diet (GFD). Combined treatment with a small dose of prednisone and diasone-sodium in addition to GFD controlled the disease of the other patient. Despite significant differences in typical cases of DH and BP, the diseases do overlap on rare occasions to form the so-called intermediate or mixed form.

Key words: Mixed form; Dermatitis herpetiformis (DH); Bullous pemphigoid (BP); Diasone-sodium; Gluten-free diet (GFD); Immunofluorescence (IF)

DH and BP are usually different clinical conditions and the criteria by which to distinguish between the two diseases are well known. The immunological differences seem to be the most important, consisting in DH of granular IgA deposits in the dermal papillae in uninvolved skin, whereas in BP, IgG and complement are found in the dermo-epidermal junction of diseased skin and in a high percentage circulating antibodies (16). Moreover, in DH the jejunal mucosa is involved; the disease is caused by an immunological abnormality associated with gluten sensitivity (13). Lastly, the response to special sulfonamides in DH and the lack of response in BP distinguish these two conditions.

Nevertheless, on the basis of clinical, histological, and particularly IF findings, some authors have observed that there may be an overlap between DH and BP (4, 5, 6, 7, 10). They do not agree with the separation of the two diseases proposed by Lever (8, 9) and Rook and Waddington (14). Transition from DH to BP and of an overlap of the two conditions was stressed by Thivolet et al. in 1969 and 1971 (18, 19). For overlap cases that cannot be classified as DH or BP, Jablonska et al. proposed in 1976 the term 'intermediate' or 'mixed' form of DH and BP (6). Some of these cases have contiguous IgA deposits along the basement membrane zone, and circulating IgA pemphigoid antibodies may be present, the so-called IgA linear dermatosis. In contrast to DH, they have no gluten-sensitive enteropathy, and a gluten-free diet is ineffective (7). In other cases both direct and indirect IF studies correspond to BP (linear IgG pattern and a positive reaction for IgG pemphigoid antibodies). Honeyman et al., among others, regard all these mixed cases as a polymorphic variant of BP (5).

This paper demonstrates immunological findings in two cases displaying the clinical and histological characteristics of both DH and BP.

METHODS

Direct IF of frozen sections from skin biopsies was performed according to standard techniques, using fluorescein-isothiocyanate-(FITC) conjugated antisera, specific for γ, μ and α heavy chains, κ and λ light chains, and complement factor C3 (obtained from DAKO Immunoglobulins Ltd., Copenhagen). A Leitz Orthoplan fluorescence microscope equipped with a Ploemopak 2.1 vertical illuminator and filter system K was employed.

HLA typing was carried out at the Tissue Typing Laboratory, The National Hospital, Oslo, Norway (Dr E. Thorsby). The HLA-ABC antigens were identified on peripheral blood mononuclear cells and the HLA-DR antigens on B lymphocytes and macrophages prepared from peripheral blood, using highly selected antisera and techniques previously described (see for example Solheim et al., 1977).

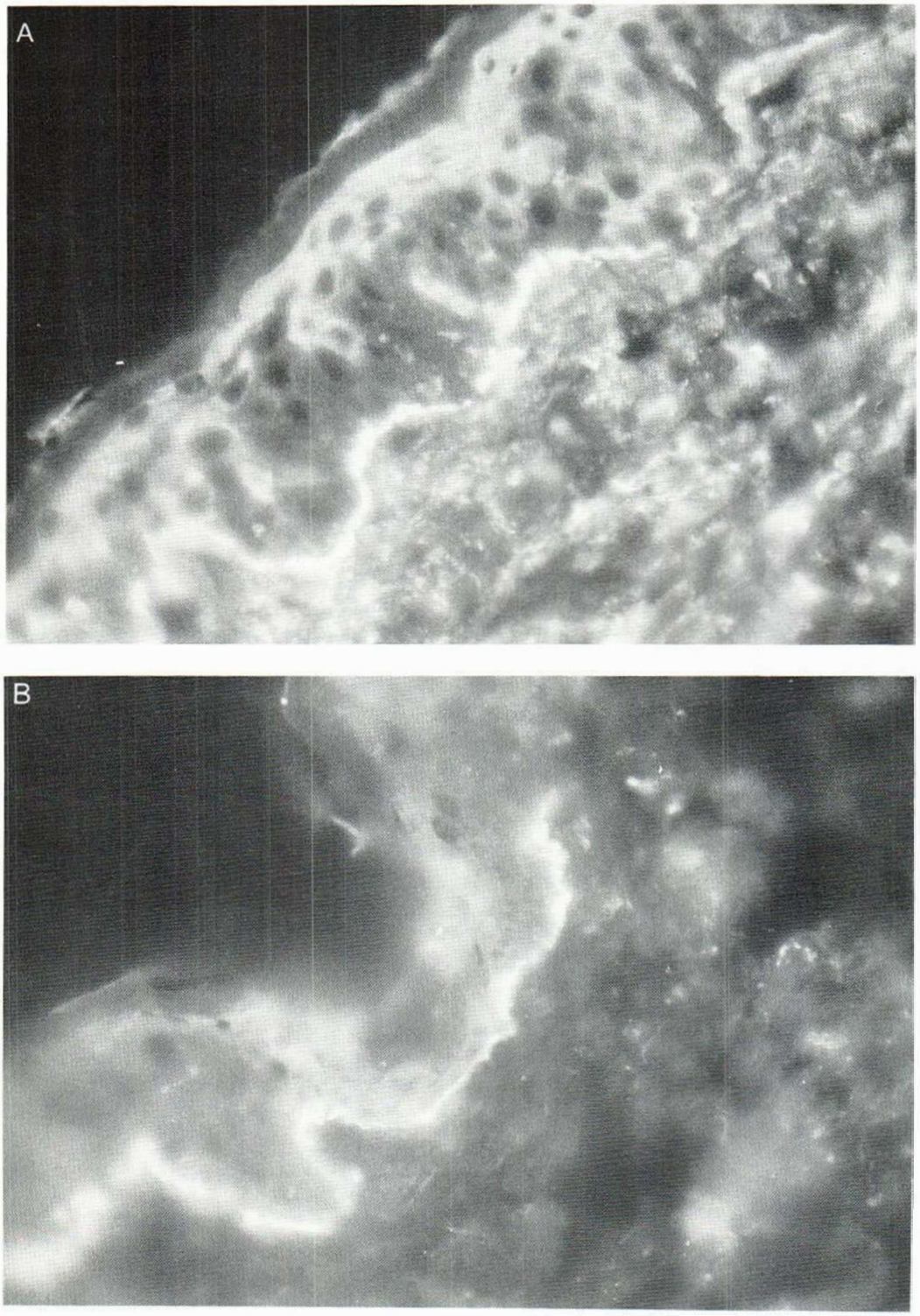
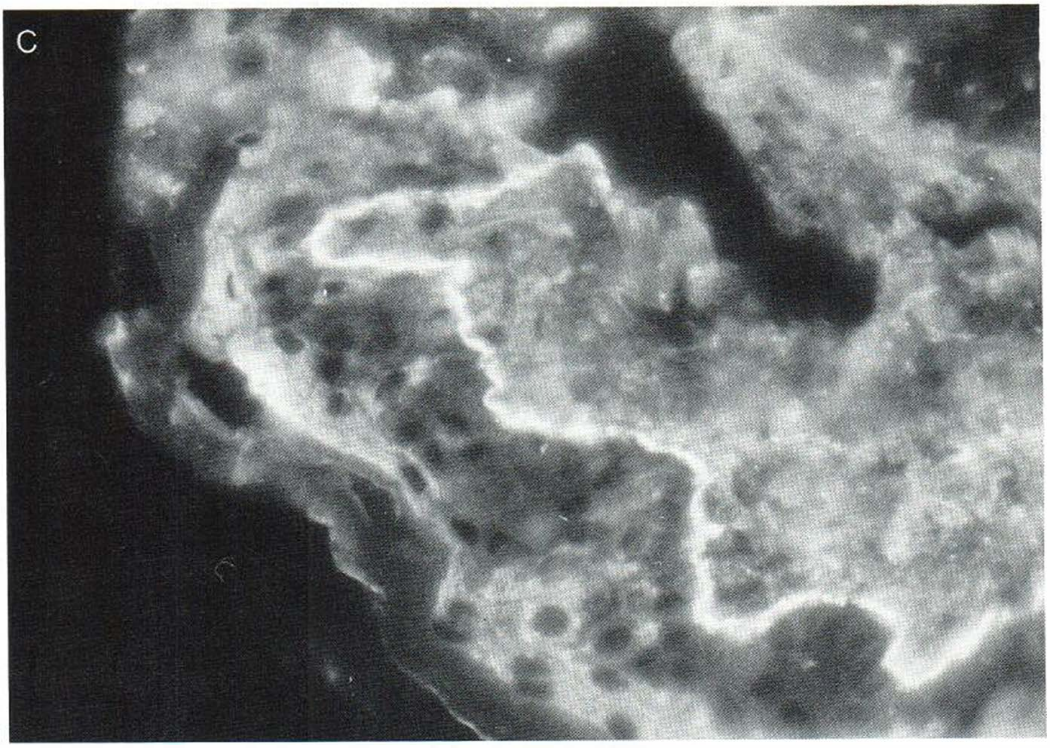


Fig. 1. Direct immunofluorescence of biopsies from case 1 (A, B) and case 2 (C, D). Biopsies stained with FITC-conjugated anti-IgG (A), anti-C3 (B), anti-IgA (C), and anti-C3 (D).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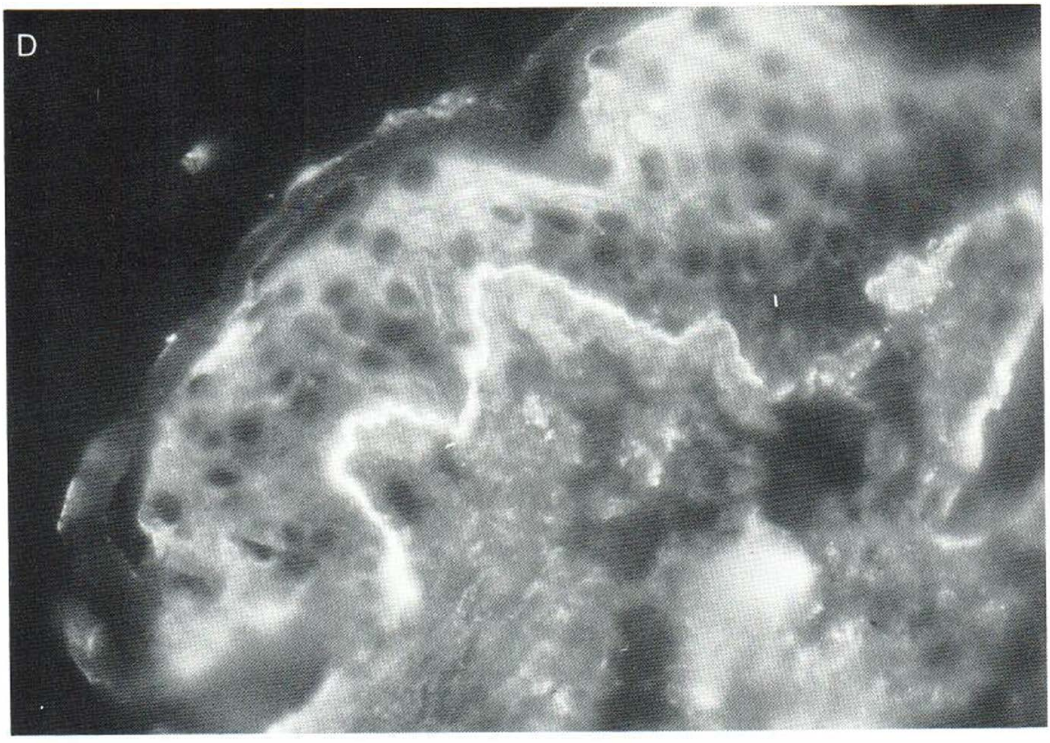
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CASE REPORTS

Case 1

A 53-year-old man was referred to our out-patient department in August 1978. It appears from information obtained that in June 1974 he developed itching, bullous eruptions on the scalp, face, neck, chest, abdomen, sacral area and both the flexor and extensor aspects of the arms.

Histological examination of diseased skin tissue in June 1974 revealed a subepidermal bulla, containing both neutrophil and eosinophil granulocytes and a microabscess at the tip of a dermal papilla. Direct IF of both healthy and diseased skin tissue revealed a fluorescent linear band of IgG and C3 along the dermo-epidermal junction (Fig 1A and B). There were no deposits of IgA and serum antibodies were not found by indirect IF. A capsule biopsy from the gut revealed normal jejunal mucosa. The diagnosis of DH was made and treatment with sulfapyridine/diasone-sodium was started. However, the patient reacted against the treatment with leukopenia and fever. Treatment was changed to prednisone, up to 60 mg daily for several months, but without response and the symptoms first improved when methotrexate 35 mg weekly and azathioprin 50 mg × 3 daily were added to the regime. The doses were gradually reduced and the patient was maintained on prednisone 20 mg daily only, which, when given periodically since then, has kept the disease in check.

In August 1978 there came a severe outbreak of the disease in the old scars. Numerous symmetrically distributed bullous eruptions could be seen in the areas described above. Otherwise he presented a typical Cushing-look.

Laboratory investigations showed a slight increase in the serum concentration of α_1-globulin (3.7 g/l) and α_2-globulin (8.2 g/l), and a decrease in the γ-globulin (5.3 g/l). All blood samples were normal, included vitamin B12 and folin acid in serum.

Repeated capsule biopsies from the gut revealed normal villous formations without signs of atrophy. Pentagastrin-test showed a markedly reduced secretion from the stomach, whereas the Schilling test, vitamin A and xylose absorption test were normal. Other findings included X-ray examination of the chest, oesophagus, duodenum, stomach, colon and urography; all proved normal. Anti-nuclear antibody (ANA) and Latex test were negative.

Histological examination of diseased skin tissue revealed a subepidermal bulla containing fibrinous exudation with neutrophil granulocytes. No eosinophil cells were seen. At the tip of a dermal papilla a microabscess with neutrophil granulocytes was observed. These findings tended to confirm the diagnosis of DH. The examination of biopsies from diseased and healthy skin tissue by direct IF revealed in both cases an intensely homogeneous fluorescent band of IgG and C3 along the dermo-epidermal junction (Fig. 1A and B). Neither IgA nor intercellular epidermal deposits of immunoglobulin nor of complement were found. These findings tended to confirm the diagnosis of BP, except that by indirect IF, using rabbit tongue as substrate, no serum antibodies were found against dermo-epidermal junction antigens. The patient was HLA-A9; W19; B8, 27; DRw3, W4.

Treatment was started with prednisone 30 mg daily and diasone-sodium 165 mg × 2 daily. The dosage of prednisone was gradually reduced to a maintenance level of 12.5 mg daily, whereas diasone-sodium was increased to 330 mg×3 daily during the same period. After 6 weeks the dosage of diasone-sodium was reduced to 165 mg×2, whereas the dosage of prednisone was mainteined at 12.5 mg daily. This medication and a GFD which has subsequently been continued, has kept the patient free from symptoms for the last 12 months.

Case 2

A 21-year-old woman had since May 1978 had an itching, slightly crusted, vesico-bullous eruption involving the scalp, face, chest, upper abdomen and the back. The patient was thought to have bullous impetigo, but failed to respond to hexachlorophene washes and topical antibiotics, which had been used for 2–3 months on the instructions of her local doctor. She was referred to our out-patient department in August 1978 with an eruption as described above.

Laboratory investigations all proved normal except for a slight increase in the serum concentration of α_1-globulin (3.8 g/l). Capsule biopsies from the gut revealed no atrophy.

Histological examination of diseased skin tissue revealed a subepidermal vesicle containing some granulocytes but without any signs of acantholytic cells. In the upper part of the demis and in some places spreading to the epidermis there was inflammatory infiltration, consisting of granulocytes, some of them eosinophil granulocytes. These findings tended to be compatible with the diagnosis of DH, and possibly even of BP.

Direct IF of diseased and healthy skin tissue revealed in both cases a linear pattern of IgA and C3 along the dermo-epidermal junction (Fig. 1C and D). No IgM or IgG was found. Indirect IF, using rabbit tongue as substrate, did not reveal serum antibodies against basement membrane or epidermal intercellular antigen. Gastric parietal-cell antibodies were found in the serum. The patient was HLA-A1,2; B8,15; CW3; DRw3.

After initial treatment with prednisone and azathioprin, the diagnosis was re-evaluated and a GFD was instituted, which has subsequently been continued. In addition the patient was given diasone-sodium daily, first 330 mg, then 990 mg, and after 6 weeks a maintenance dose of 330 mg. The patient has remained symptom-free for the last 12 months.

DISCUSSION

Notwithstanding the IF findings, in case 1 the diagnosis of severe DH had been established on the basis of the clinical and histological findings, yet a GFD had not been tried and the treatment with sulfones only had failed. The patient had thus been maltreated with relatively large doses of azathioprin, methotrexate and prednisone for 4 years. Combined treatment with prednisone and diasone-sodium in small doses and additional FGD has now

kept him free from lesions. In case 2 the diagnosis of BP was made on the basis of the IF findings. The linearity of the deposits suggested the presence of antibody directed against an antigen in the dermoepidermal zone, and should therefore indicate BP. Since the antibodies were not found in the serum, one explanation could be that all antibodies were bound in situ in the skin. After initial treatment with prednisone and azathioprin, the diagnosis was reevaluated, and subsequently a GFD and small dosis of diasone-sodium has kept her free from lesions.

It must be stressed that in both cases a linear, non-granular fluorescence pattern was seen. In case 1 direct IF of both healthy and diseased skin tissue revealed a fluorescence band of IgG and C3 along the dermo-epidermal junction, and in case 2 direct IF of healthy and diseased skin tissue revealed in both cases a linear pattern of IgA and C3 along the dermo-epidermal junction. Linear immune deposits consisting exclusively of IgA at the basement membrane zone are regarded by some authors as not unusual in cases of DH (1, 3, 7, 15), though van der Meer, among others, regards such cases as miscellaneous, or even atypical BP (11, 12), and Honeyman et al. apply the term polymorphic pemphigoid (5). Anti-basement membrane antiboides were not found in either case. In both cases the jejunal mucosa appeared normal. However, the characteristic jejunal changes are not detectable in all cases of DH and therefore the biopsy, if negative, should be repeated. A diagnosis of gluten-sensitive enteropathy should not then be excluded when the mucosa appears normal. Fry et al. regard increased lymphocytic infiltration of the epithelium of the small intestine as a more sensitive marker than the macroscopic and histological features, and consider that this lymphocytic infiltration may represent an underlying immunological reaction to gluten (2). On the other hand, it may be, as supposed by Jablonska and Chorzelski, that patients with IgA linear dermatosis—in contrast to DH—have no gluten-sensitive enteropathy and that GFD is ineffective (7). It is impossible to say if the GFD in our cases has been of any consequence for the remission of the disease, but it has been continued for fear that a relapse of the symptoms might occur if discontinued.

Several studies have revealed a strong association between the HLA-antigen DRw3 and DH. In previous studies from Norway, 97 % of 29 patients with DH were found to carry DRw3, compared with 25 % of healthy controls (17). The HLA investigations showed that both our patients carried DRw3. Clinical differentiation between DH and BP may be difficult. Even in BP confirmed by IF studies with lack of a response to sulfones and a normal jejunal mucosa, the lesions can often resemble DH with severe itching. On the other hand, in some patients with classic DH during relapse, typical large bullae as seen in BP may occur. The response to sulfones is also a very doubtful diagnostic criterion, because some cases of BP may also respond. IF studies are of basic diagnostic importance, but when a continuous fluorescence pattern is observed, especially if IgG or IgM is present in addition to prevailing IgA, distinction from BP without circulating antibasement membrane antibodies may be difficult, or even impossible. Cases of benign chronic bullous dermatosis of childhood have recently been described in which linear IgA deposits along the basement membrane zone were the predominant or sole IF finding (10). However, jejunal biopsy findings have not yet been reported adequately, and HLA studies on patients and their families ought also to be made to clarify and classify this disease. In spite of an evident distinction between DH and BP in most cases, mixed or overlap cases do occur.

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