

EPIDERMOLYSIS BULLOSA ACQUISITA AND CROHN'S DISEASE

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Abstract. A patient with epidermolysis bullosa acquisita (EBA) associated with Crohn's disease is presented. The clinical, histological and immunological findings were in keeping with previous reports. However, clinically normal skin and mucosa exhibited deposits of IgG and C3 in the basement-membrane zone. These deposits remained unchanged during the treatment period. It is therefore suggested that immunological mechanisms are implicated in pathogenesis of the disease.

Key words: Epidermolysis bullosa acquisita; Crohn's disease; Immunglobulins, complement

Epidermolysis bullosa is usually an inherited disease, starting in early life. It is characterized by erosions, bullae and dystrophic changes with superficial mild scarring and milia formation localized to sites of insignificant mechanical trauma, predominantly on the hands, elbows, feet and knees.

According to Lever & Schaumburg-Lever (6) the disease includes:

1. Epidermolysis bullosa simplex (dominant).
2. Epidermolysis bullosa of Cockayne, of the hands and feet (dominant).
3. Dominant-dystrophic epidermolysis bullosa.
4. Recessive-dystrophic epidermolysis bullosa.
5. Epidermolysis bullosa lethalis (recessive).

In addition there is a rare non-hereditary form, epidermolysis bullosa acquisita (EBA), which occurs in adult life and presents the clinical picture of dystrophic epidermolysis bullosa yet with no evidence of hereditary transmission.

EBA is a disease often associated with systemic disorders (6, 7, 13). Its association with Crohn's disease has been reported five times (4, 5, 9, 12, 13).

CASE REPORT

A 19-year-old man was admitted to the Department of Dermatology in November 1976 because of a bullous cutaneous disease. On the face and neck he had fresh small and large bullae containing a yellow fluid, erosions

with crusted remnants of earlier bullae and superficial reddish scars with prominent milia. The dorsum of the hands and fingers, the left elbow and both knees showed small irregular violaceous superficial atrophic scars with numerous milia. The toenails and one of the fingernails of the left hand showed dystrophic changes (Fig. 1). Erosions and bullae were also present on the lips, buccal mucosa and the tongue, and there was desquamation of the gingival mucosa. The first lesions developed in August 1975, appearing after minor mechanical trauma, and leaving scars on the face, hands, fingers and feet.

Laboratory data. Haemoglobin 9.3-12.2 g/dl, sedimentation rate 32-23 mm/h, white blood count $10.7-7.0 \times 10^9/l$ with a normal differential count. Bilirubin, alkaline phosphatase, gammaglutamyl-transferase, alanin aminotransferase, protein electrophoresis and electrolytes in serum were all within normal ranges. LE cells and antinuclear factor were not demonstrated. The serum levels of immunoglobulins C3 and C4 were within normal levels. The percentages and total counts of T and B lymphocytes were within normal ranges. The Pirquet reaction was negative as before the onset of the disease. Uroporphyrins and porphobilinogen were not demonstrated. Occult blood in faeces was repeatedly positive.

Gastrointestinal examination. X-ray of the stomach, duodenum and intestines showed several duodenal ulcers and a 4 cm long stricture distal to the bulb. In the distal part of the descending duodenum the lumen was rigid, with a short stricture. The mucosal appearance of the jejunum was normal, whereas there was a 20 cm long strictured segment in the distal part of the ileum. In the ascending part of the colon multiple small ulcers and cobblestone pattern of the mucosa was found.

Gastroduodenoscopic examination revealed moderate thickening and injection of the mucosa of the distal esophagus, but no ulceration. The mucosal pattern of the stomach appeared normal. The duodenal bulb showed marked inflammatory changes, with oedema, injection and two deep linear ulcers. Distal to the duodenal bulb the lumen was strictured. Biopsies were taken from the duodenal bulb for morphological and immunological studies.

Sigmoidoscopic examination showed no pathologic changes in the mucosa in the rectum. Inspection revealed an anal fissure and a small broad-based perianal oedematous tumour.

The results of the absorption studies indicated normal function of the ileum as well as the jejunum. The fecal fat

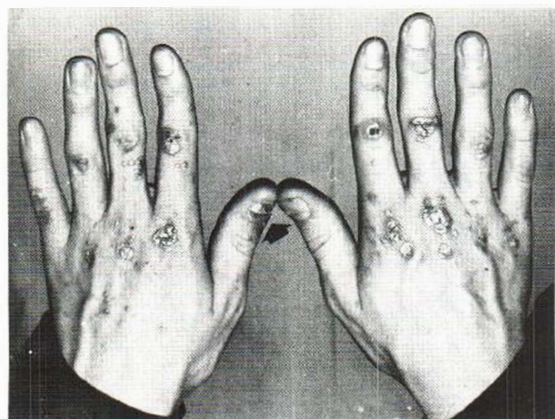


Fig. 1. Epidermolysis bullosa acquisita with scars, milia and a dystrophic nail (arrow).

excretion was 1.6 g/24 h (normal <6.0/24), and the Schilling test was 16% (normal >8.0). The breath test for altered bile acid metabolism as well as the *D*-xylose absorption test were normal.

Histological examination. Biopsy specimens taken under local anesthesia were fixed in 10% neutral formaldehyde, paraffin-embedded and stained with haematoxylin and eosin (HE), periodic-acid Schiff (PAS), elastin Van Gieson, alcian blue, (pH 2.5) and 1% crystal violet (pH 2.9). Sections from skin biopsy specimens of the dorsum of hand showed a large subepidermal bulla containing a few inflammatory cells, (Figs. 2 and 3) but no acantholytic cells. In PAS-stained sections the basement membrane at the periphery of the bulla appeared split, with one part attached to the epidermal roof and one to the dermal floor.

The underlying connective tissue showed mild inflammation, several small cysts lined with keratinizing epithelium (Fig. 2) and relatively few elastic fibres. Staining for amyloid and acid mucopolysaccharides could not be demonstrated by using crystal violet or alcian blue staining.

Examination of the biopsy specimens of the oral mucosa revealed similar findings, except for the lack of epidermal cysts. The duodenal biopsy specimens showed an intense infiltration of lymphocytes, plasma cells, histiocytes and eosinophils in the mucosa as well as in submucosa and muscularis. No granulomatous foci or multinucleated giant cells were found.

Immunological examinations. Biopsy specimens from skin, oral and duodenal mucosa were also frozen in pre-chilled isopentane in liquid nitrogen. Immunofluorescence procedures were performed as described previously (14). Briefly, cryostat sections (4–6 μ m) were treated for 30 min at room temperature with fluorescein–isothiocyanate (FITC) labelled rabbit antisera against human IgG, IgA and IgM (C3) (batches 075 015, 124) (Dakopatts, Denmark) and IgM and fibrinogen (batches 693M, 583Z) (Behringwerke AG, West Germany) in direct immunofluorescent studies.



Fig. 2. Micrograph of section from the dorsum of the hand showing subepidermal bulla and milia. (HE $\times$ 70).

The antisera were tested for specificity in double precipitation in agarose and immunoelectrophoresis and used in the test as described previously (14). The working dilutions of the dissolved conjugates were 1:4. In indirect immunofluorescence, skin tissue sections from a healthy individual were treated for 30 min at room temperature with heat-inactivated serum (56°C/30 min) and after washing incubated for the same period of time with a FITC-labelled antiserum against IgA/IgG/IgM (batch 602B) (Behringwerke AG, West Germany).

Direct immunofluorescence of the skin sections revealed a thick granular continuous band of IgG, C3 and fibrinogen in the basement membrane zone adjacent to the blisters (Fig. 4). IgG and C3 were also found along the basement membrane of the hair follicles and the sebaceous glands. Examination for the oral mucosa adjacent to the blisters showed a similar subepithelial band of IgG, IgA and C3. In addition, deposits of C3 were found in the walls of small vessels.

The floor of the blister on the skin as well as on the oral mucosa contained diffusely localized deposits of IgG, C3 and fibrinogen. Biopsy specimens from various locations of clinically normal skin contained deposits of IgG and C3 along the basement membrane zone.

Normal skin from 2 healthy individuals and 4 untreated patients with Crohn's disease (but without dermatological manifestations) served as controls. Deposits of immunoglobulins and complement could not be demonstrated.

Tissue sections of the duodenal mucosa revealed numerous immunoglobulin containing cells in badly in-



Fig. 3. Subepidermal bulla of the hand with sparse inflammation in the connective tissue. (HE $\times$ 320).



Fig. 4. Fluorescent micrograph from clinically normal skin with fine granular deposits of IgG in the basement membrane zone. Note early formation of bulla (arrow). ($\times$ 92).

flamed areas, but no band-like deposits similar to those found in the skin and oral mucosa. Indirect immunofluorescence with autologous serum did not reveal antibodies against epithelial intercellular antigens or the basement membrane zone.

After treatment with prednisone and azathioprine for 7 months, there was nearly complete remission of the lesions in the proximal duodenum, and slight remission of the skin lesions. Direct immunofluorescence of the involved and uninvolved skin was repeated during resolution of the disease and identical results obtained.

DISCUSSION

The case presented fulfils the criteria for the diagnosis of EBA, both clinically, histopathologically and by the lack of bullous disorders in the family (13). Other bullous disorders, the porphyrias, bullous pemphigoid, pemphigus, dermatitis herpetiformis and bullous drug eruptions were excluded. In porphyria the clinical picture may mimic that of EBA, but lacks involvement of

the oral and intestinal mucosa. Immunological investigations of this disorder have revealed deposition of immunoglobulins, primarily IgG, but also IgA and IgM, similar to that seen in EBA in light-exposed skin—but not in unexposed skin (3). Furthermore, porphyria was excluded through repeatedly negative investigations for uroporphyrins and porphobilinogen in urine and stool.

The immunological findings in perilesional skin in our patient resembled those seen in bullous pemphigoid. However, in bullous pemphigoid, circulating antibasement membrane zone antibodies are usually present and deposits of immunoglobulins and complement factors are not seen in non-lesional skin, in contradistinction to the findings in our patient (10). Furthermore, in the present case the basement membrane zone deposits were granular, as opposed to the linear deposits characteristic of bullous pemphigoid.

The results of radiological and endoscopic ex-

aminations revealed that, in addition to EBA, the patient also suffered from Crohn's disease, in keeping within previous reports (4, 5, 9, 12, 13). Other dermatoses such as erythema nodosum, erythema multiforme, pyoderma gangrenosum, cutaneous polyarteritis nodosa have also been observed in connection with intestinal manifestations of Crohn's disease (2, 7, 13, 15). In addition Crohn's disease of the intestine may be associated with skin lesions which histopathologically exhibit the characteristic features of this entity (8, 11, 16).

The immunological findings in skin tissue specimens of skin lesions were consistent with the results reported by others (5, 9). In addition, we found deposition of IgG, C 3 and fibrinogen in the form of a fine granular layer in the basement membrane zone in clinically normal skin and oral mucosa. This is similar to the picture seen in systemic lupus erythematosus (1), which was excluded both clinically and histopathologically in the present case.

The etiology of EBA as well as Crohn's disease still remains obscure. Presence of these two disorders in the same patient may be accidental, but may also suggest a systemic condition involving immunological mechanisms. Vasculitis, with C3 in vessel walls and granular deposits of Ig and C3 in the basement membrane zone suggest that participation of immune complexes may be involved in the pathogenesis.

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