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Mixed Bullous Disease with Labile Erythrocyte Sedimentation Rate

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Abstract. A woman, aged 66, fulfilled all the usual criteria of dermatitis herpetiformis. Subsequently, she developed circulating IgA and IgM basement membrane zone antibodies, a labile erythrocyte sedimentation rate (ESR), and the clinical picture changed to one of bullous pemphigoid. Her labile ESR was obviously caused by a factor related to the erythrocytes. Direct Coombs test was positive.

Key words: Mixed bullous disease; Dermatitis herpetiformis; Bullous pemphigoid; Labile erythrocyte sedimentation rate

In most cases, differentiation between dermatitis herpetiformis (DH) and bullous pemphigoid (BP) is feasible, based on the clinical findings, biopsies of skin and jejunum (4), immunofluorescence test (IFT) (8), therapeutic response to sulphones in DH, and HLA typing (7). However, coexistence or overlap of DH and BP may occur ("mixed bullous disease") (3). This article present a patient with the clinical picture of DH which subsequently changed to BP accompanied by a highly labile ESR.

CASE REPORT

A 66-year-old woman had suffered from coeliac disease since the age of 17. When hospitalized in September 1977, she had developed a pruritic polymorphic vesiculo-bullous dermatitis on her limbs, abdomen and around the natal cleft. The clinical diagnosis of DH was confirmed by cutaneous biopsy of the pathological skin, and direct IFT of involved and "normal" skin, both showing linear deposition of IgA along the basement membrane zone (BMZ). Suction biopsy of the jejunal mucosa revealed subtotal villous atrophy, and absorption of an oral vitamin A test dose was pathologically impaired. A daily oral dose of 100 mg dapsone healed her skin lesions within 2 weeks. She was discharged on a dose of 50 mg dapsone daily and an iodine- and gluten-free diet.

Recurrence of the exanthema in Jan. 1978 led to a new direct immunofluorescence test (IFT) of involved and "normal" skin; both showing a linear, continuous band-like fluorescence of IgA along the BMZ. Unexpectedly, the indirect IFT on this occasion was found to be positive, demonstrating circulating antibody of the IgA class (titre: 1/128) against BMZ in sections from monkey oesophagus. In addition, a considerable variation in ESR values was noted. On 4 consecutive days, the following values were recorded: 105, 5, 80 and 5 (mm/h).

Increase of the dapsone dose to 100 mg daily, supplemented with nicotinic acid 300 mg daily, alleviated the skin symptoms for some weeks.

However, in March 1978, typical clinical signs of BP appeared, in the form of non-pruritic large and tense bullae on the scalp, neck, axillary folds, abdomen and limbs. A new indirect IFT showed circulating IgA and IgM antibodies against BMZ (titre: 1/32). The ESR estimations continued to fluctuate widely (see below). Direct Coombs test was positive (++).

Dapsone medication was discontinued and oral prednisone treatment with a dose of 60 mg daily was started on 7th April 1978. A week later, the prednisone dose was increased to 80 mg daily, and the daily medication of 300 mg nicotinic acid was continued. During the first 2–3 weeks of this therapy, the skin lesions resolved. The circulating antibodies disappeared and the ESR was stable within normal limits. The prednisone therapy was then gradually reduced over a period of 5 weeks to 45 mg daily, at which point dapsone (100 mg daily) was added.

The patient was discharged on 9th June 1978 with completely resolved skin lesions and was kept in remission on daily oral doses of 15 mg prednisone and 50 mg Dapsone, supplemented with 300 mg nicotinic acid and diet.

INVESTIGATION OF THE LABILE ESR

Sufficient blood for 10 ESR tests was collected by venepuncture and the 10 tests were performed simultaneously at room temperature by the Sedimat® system (disposable PVC tubes) (2). All the tests gave different results, varying from 4 to 72 mm/h (Fig. 1). Another series of 10 ESR tests was carried out by the Westergren method (9) (glass tubes), but the results varied similarly. Tests performed at 37°C showed the same lability (range: 11–70 mm/h). However, at a temperature of 4°C, lability of the ESR did not occur; 10 tests at this temperature were within the range 2–4 mm/h. A control series of 10 tests with blood from a healthy donor was carried out (both by the Westergren and the Sedimat system), in order to exclude possible errors in method and technique. No lability could be detected.

In order to study whether the labile ESR was caused by factors in the plasma or on the erythrocytes, the following

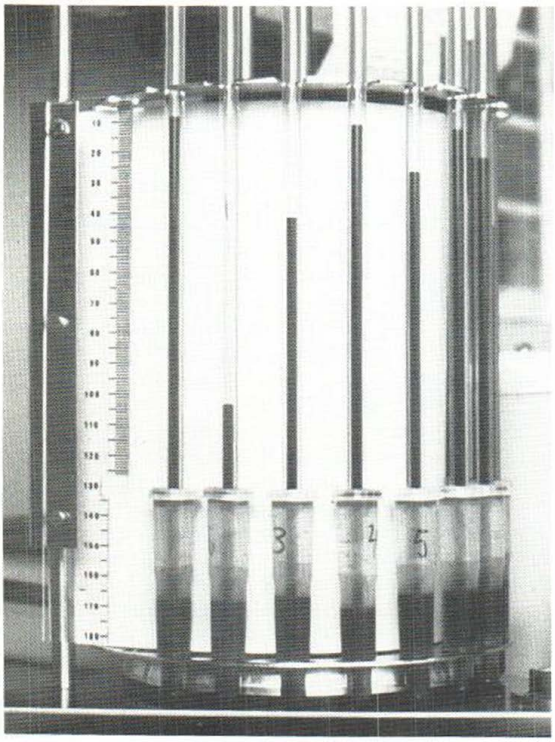

Fig. 1. Ten ESR tests performed simultaneously. From a patient with "mixed bullous disease". All test tubes showed different results.

experiment was performed: Washed erythrocytes from the patient were mixed with the plasma of a healthy control person with the same ABO blood group, while another solution was obtained using patient's serum mixed with washed erythrocytes from the control person. Both suspensions were then adjusted to a haematocrit value corresponding to the haematocrit reading of the original blood of the patient. Labile ESR was only seen in the suspension containing the patient's erythrocytes mixed with normal plasma, but not seen in the mixture of the patient's plasma with normal erythrocytes. Hence, the causative factor must have been on the patient's erythrocytes.

OTHER LABORATORY FINDINGS

Serum electrophoresis on cellulose acetate showed a polyclonal increase of gamma-globulins. Quantitative estimation: IgA: 5.3 g/l (reference values 0.5–3.5 g/l), IgG: 26.9 g/l (reference values 7.5–15.0 g/l). The haptoglobin, serum-iron, LD and reticulocyte levels were normal during dapsone medication, in contrast to the haemoglobin levels (see below) which varied between 10.7 and 13.8 g/100 ml (reference values 11.5–15.5 g/100 ml).

While the direct Coombs test was positive during the period of ESR lability, monthly assessments after the commencement of prednisone therapy showed a gradual reduction in titre until finally after 3 months, the direct Coombs test became negative. HLA-antigen studies showed presence of DRw 3 together with HLA-A_2, B7 and W35.

DISCUSSION

The borderline between classical DH and classical BP is quite distinct, though transitional cases do occur. Circulating auto-antibodies are usually not found in DH, although occasional cases have been reported with circulating BMZ antibodies of the IgA class (5). Approximately 85% of patients with BP have circulating antibodies against epidermal BMZ, usually of the IgG class, but IgM, IgA and Ig E have also been involved in a small number of patients (6). Our patient had coeliac disease for many years before she developed typical DH which responded to dapsone. Later on, she developed typical BP, with circulating IgA and IgM BMZ antibodies, and prednisone treatment became necessary. These findings can be interpreted as indicating a change from DH to BP or as evidence for the coexistence of both diseases (mixed bullous disease).

During the active stage, the ESR was very labile. The association of this phenomenon with bullous disease has not, to our knowledge, been previously reported. We believe that the labile ESR was caused by some coating of the erythrocytes with autoantibodies, complement factors, or immune complexes. It is interesting that the lability disappeared at a temperature of 4°C, and this seems to exclude the possibility of cryoglobulins being involved. Following 1–2 weeks of prednisone medication, the ESR became stable, within normal limits. However, 3 months elapsed before the Coombs test finally became negative. Hence, the corticosteroid therapy must have prevented the undue tendency to erythrocyte aggregation in vitro, whereas the coating, rendering Coombs test positive, remained on the red cells until their population had been renewed.

During dapsone medication, but previous to the administration of prednisone, our patient had a moderate anaemia (Hgb: 10.7 g/100 ml and erythrocytes: 2.9×10^{12}/l). It is well known that haemolytic anaemia can result from dapsone treatment. Consistent signs of haemolysis did not occur, however. It is more likely that her moderate anaemia was due to extravascular destruction of coated erythrocytes by phagocytosis within cells of the reticulo-endothelial system.

The lability of ESR in the present case seems to have been correlated to the disease activity. Similar labile ESR results have previously been recorded in 2 out of 10000 presumably healthy blood donors (1). In these cases, the lability occurred only at room temperature and not when the tests were carried out at 4°C and 37°C.

It would be of interest when investigating patients with bullous diseases of the DH/BP/pemphigus group and other disorders with autoimmune phenomena, and particularly those with a positive Coombs test, to look further into the question of labile ESR by more routinely carrying out a multitude of ESR tests at the same time.

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Congenital Localized Skin Defect and Epidermolysis Bullosa Hereditaria Letalis

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Abstract. Epidermolysis bullosa hereditaria letalis (Herlitz) rarely appears with all the clinical characteristics originally described as belonging to the syndrome. Besides the blistering of the skin and mucous membranes in the oral cavity, the case presented showed dystrophic nails, congenital localized skin defects with hypoplasia of underlying structures and a rare but characteristic malformation of the foot of the affected extremity. No scar formation occurred before death at the age of 6 months. Histological examination of the blisters showed separation between the basement membrane and the cell membrane of the basal cells. In areas of skin defects, normal appearing hair follicles and sweat glands were seen. The relation of the syndrome to Bart's syndrome is discussed.

Key words: Congenital skin defect; Epidermolysis bullosa hereditaria letalis; Electron microscopy

Congenital localized absence of skin is a rare defect. In the majority of cases there is a solitary coin-sized lesion near the vertex of the scalp, usually involving the skin and subcutaneous tissue (8, 9). Occasionally, congenital skin defects are localized on the trunk or the extremities, where they tend to be more superficial, with a symmetrical distribution most frequently affecting the lower legs. This form may be associated with epidermolysis bullosa. In 1966 Bart (2) reviewed the literature on the subject and found 19 reports of congenital localized absence of skin associated with blistering of skin or mucous membranes or both. The skin defect involved the extremities in all but one patient; no patients had scalp lesions. Twelve cases presented in four of the nineteen reports were examples of the epidermolysis bullosa hereditaria letalis (Herlitz, 1935) type of epidermolysis. This disease entity was re-established in 1974 by Pearson (7) who presented the clinical and histological characteristics of five cases. However, in only four cases originally described by Herlitz has the syndrome been as-