A newborn with bullous pemphigoid associated with linear IgA bullous dermatosis

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SUMMARY

A 16-day-old boy was admitted to our clinic with localized blisters on the neck, cheeks, earlobes, and oral cavity and with erythema on the toes, in addition to poor weight gain and respiratory distress. A physical examination revealed several erythematous plaques with tense bullae, multiple vesicles, and erosions on the left toes, neck, earlobes, and face as well as erosive lesions on the anterior part of the oral cavity, lips, and buccal mucosae. A bronchoscopic examination revealed bullous lesions in the upper respiratory tract and on the epiglottis. A skin biopsy suggested a diagnosis of bullous pemphigoid (BP). Because of the severe mucosal involvement, further investigations including various immunological techniques were performed. The case was diagnosed as BP associated with linear IgA bullous disease (LAD). Complete remission without any scarring was achieved after three weeks of oral methyl prednisolone treatment. A correct differential diagnosis of bullous diseases is important for determining the prognosis and expected response to treatment. To our knowledge, this is the first case of BP associated with LAD reported in literature.

KEY WORDS

newborn, bullous pemphigoid, linear IgA bullous disease, mucosal involvement

Introduction

Autoimmune subepidermal blistering diseases are considered prototypical bullous disorders because of their well-defined autoantibody-mediated development or pathogenesis. In all autoimmune subepidermal blistering diseases, antibodies bind to specific antigens in the dermo-epidermal junction. This immune deposition leads to complement activation and inflammatory cell chemotaxis, which is followed by a loss of adhesion at the dermal-epidermal junction and blister formation. The end result is a loss of skin architecture. Differentiation of bullous diseases may be difficult. In addition, more than one disease can occur at the same time, leading to a complex presentation. The diagnosis of a bullous disorder depends upon the combination of clinical and histologic features, the results of direct and indirect immunoûuorescence, and the appearance of antibodies against a specific antigen.

Bullous pemphigoid (BP) and linear IgA bullous disease (LAD) are autoimmune bullous diseases with subepidermal blisters and are characterized by anti-basement membrane zone (BMZ) antibodies of IgG and IgA classes, respectively (1, 2). These diseases are very

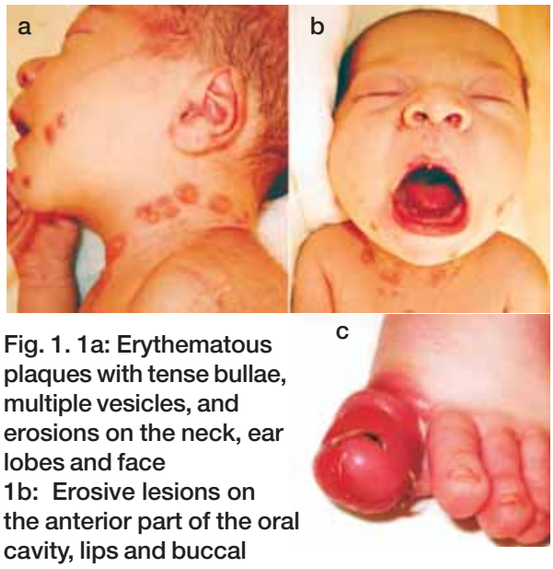

Fig. 1. 1a: Erythematous plaques with tense bullae, multiple vesicles, and erosions on the neck, ear lobes and face
1b: Erosive lesions on the anterior part of the oral cavity, lips and buccal mucosae

rare in infants, and most cases occur in school-aged children (usually before puberty) (3, 4). A correct differential diagnosis of bullous diseases is important for determining the prognosis and expected response to treatment.

Here we present the case of an infant with BP associated with LAD showing severe mucosal involvement, who was successfully treated with oral corticosteroid.

Case Report

A previously healthy 16-day-old boy born to nonconsanguineous, healthy parents was admitted to our clinic with localized blisters in the neck, cheeks, earlobes, and oral cavity and with erythema on the toes, in addition to poor weight gain and respiratory distress. He had only been vaccinated against hepatitis B virus (single dose) and his family history was unremarkable. His mother had noted the first erythematous skin lesions with blisters on the left toes, face, neck and lips 10 days previously, and the blisters had healed without scarring.

Physical examination revealed several erythematous plaques with tense bullae, multiple vesicles, and erosions on the left toes, neck, earlobes, and face (Figure 1a), as well as erosive lesions on the anterior part of the oral cavity, lips and buccal mucosae (Figure 1b). In addition, his left first toe was erythematous and swollen (Figure 1c). He was dyspneic, tachypneic, and had rough rhonchus. A chest X-ray was normal. A bronchoscopic examination revealed bullous lesions in the upper respiratory tract and on the epiglottis. Because he refused oral feeding, an esophagoscopy was performed that revealed numerous bullous lesions on the esophagus. A gastrostomy tube was inserted for feeding.

Routine laboratory tests showed hemoglobin of 12.3 g/dl, white blood cell count of 9390/µl, with 18% neutrophils, 12% eosinophils, 8% monocytes, 62% lymphocytes and a normal C-reactive protein level. Bacterial and viral cultures as well as herpes simplex virus staining were negative. The serum C3, C4 and immunoglobulin levels were normal. The antinuclear antibodies were positive in the patient and his mother.

A skin biopsy specimen taken from the edge of an intact skin area showed subepidermal blisters containing neutrophils and eosinophils as well as a normal lower layer of the dermis (Figure 2). Direct immunofluorescence showed a weak linear deposition of IgG and C3c at the dermoepidermal junction. Depositions of IgA and IgM were not detected.

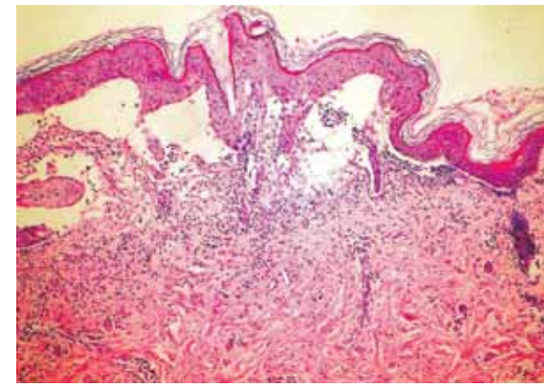

Fig. 2. Histological study of the perilesional skin shows a subepidermal blister with an infiltration mainly of eosinophils and neutrophils in the cavity and the superficial dermis (hematoxylin and eosin stain, × 40).

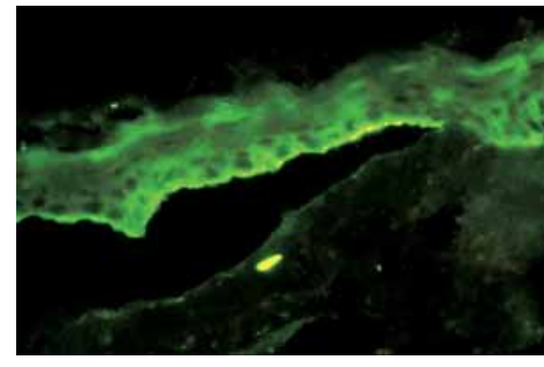

Figure 3. With direct immunofluorescence of 1-mol/l NaCl-split skin. IgA positive on the epidermal side, IgA negative on dermal side (× 200).

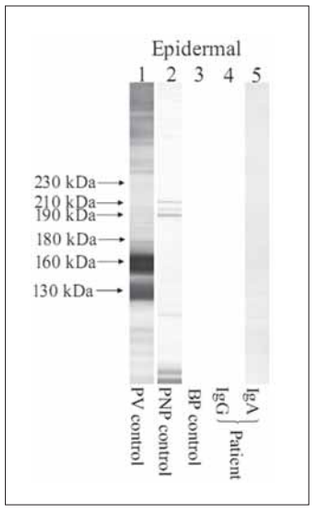

Fig. 4a. Immunoblotting of EDTA separated from normal human dermal extract. IgG reacted with BP230 by immunoblotting of epidermal extract, and was shown weakly positive with BP180 by ELISA.

Standard indirect immunofluorescence (IIF) did not demonstrate IgG and IgA anti-BMZ antibodies. IIF using 1M NaCl split skin showed IgA anti-BMZ antibody reactive with epidermal side (Figure 3), but IgG was negative. By immunoblotting using epidermal extract, IgG reacted with BP230 but not with BP180. However, no antigens were detected for IgA by immunoblotting. Immunoblotting using recombinant protein of the BP180 NC16a domain did not show positive reactivity for both IgG and IgA. There were no results suggesting epidermolysis bullosa acquisita or anti-p200 pemphigoid with immunoblotting using dermal extracts. The ELISA of recombinant protein of the BP180 NC16a domain was in the gray zone (BP180 index 18.24). The ELISA for BP230 was negative. Therefore, although the reactivity was relatively weak, our case was diagnosed as BP associated with LAD. Alternatively, this case could be diagnosed as having linear IgA/IgG bullous dermatosis.

Treatment with oral methyl prednisolone (1mg/kg/day) resulted in remarkable clinical improvement of the skin and mucosal lesions without scarring within the first week. Therefore, the dosage was quickly tapered and finally discontinued, when complete remission was achieved after three weeks of therapy. The patient was still in remission six months after treatment. The gastrostomy tube was removed two months later, because the mucosal and dermal lesions did not recur.

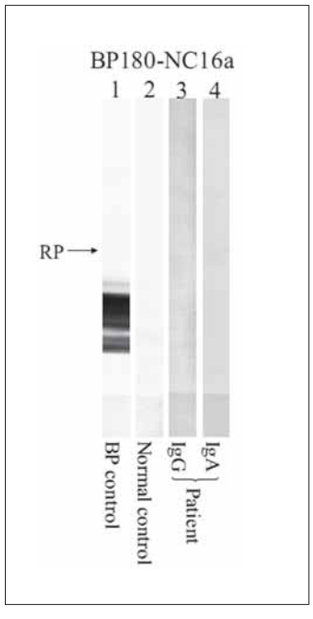

Fig. 4b. Immunoblotting of the fusion protein of the 180-kDa BP antigen NC16a domain. The patient's serum (for IgG and IgA) and normal serum did not react with the fusion protein; the BP control serum clearly reacted.

Discussion

In our case, direct immunofluorescence showed deposition of only IgG and C3c. IIF using a normal human skin section revealed no positive reactivity. IIF using a 1M NaCl-split human skin section detected only IgA anti-BMZ antibodies reactive with the epidermal side of the split, suggesting the diagnosis of lamina lucida-type LAD. On the other hand, immunoblotting of normal human epidermal extracts revealed only IgG antibodies to BP230, but not BP180. The BP180 ELISA was in the gray zone (18.24), and BP230 ELISA was negative. These results suggested the diagnosis of BP. Other immunoblot examinations including normal human dermal extracts, recombinant protein of BP180 NC16a, and concentrated supernatant of culture medium of HaCaT cells were all negative. Finally, we diagnosed our patient as BP associated with LAD.

BP is rare in childhood. However, BP is still the most common IgG-mediated subepidermal bullous disease in children. The classical clinical features of BP include widespread tense blisters arising on erythematous or clinically unaffected skin and mucous membranes. The clinical, histopathologic, and immunologic features of childhood BP are distinct from adult BP. In childhood BP, mucous membrane involvement is more common than in adult BP (1–4, 6). All affected infants 1 year of age or younger reported to date had marked palmoplantar and facial involvement (4, 6, 7). In a report from Israel, among 78 reported children with BP, 42 cases (53%) occurred in the first year of life (8). The age at initial infantile BP symptoms was the first 6 months of life in 78.8% patients (13). When BP occurred in an infant, there was considerable clinical and histologic overlap with other acquired or congenital blistering disorders (10, 12, 16).

Childhood BP is an immune-mediated disease that is associated with a humoral and cellular response directed against two autoantigens; BP230 and BP 180 (2, 4, 8, 9). Recently a new autoantigen, BP antigen 190, has also been shown (10–12). Immunochemical and immunoelectron microscopic studies have revealed in-

tracytoplasmic BP230 and transmembranous BP180 in hemidesmosomes (9–12). In infantile BP, antibodies may be transferred to the fetus passively during pregnancy (11). BP antigens have been shown to present within the lamina lucida and hemidesmosomes of the basal keratinocytes (9, 10, 12–16). Recent molecular biological studies have indicated that the NC16a domain of the BP 180 is the most immunogenic domain (9, 10). Our case reacted with BP230, but not with BP180 by immunoblotting using normal human epidermal extracts.

A recent study showed that the presence of autoreactivity against both the NC16a and carboxy terminal domains was more frequently detected in BP patients with mucosal lesions (4, 15). Levels of IgG autoantibodies against the BP 180 NC16a domain have been shown to be clearly related to disease activity in adult BP (17). However, in our case, immunoblotting using the BP180 NC16a domain for IgG and IgA was negative. For our case, among all immunoblotting techniques, only IgG anti-BP230 antibodies were positive.

Patients with BP and LAD have a dual IgG and IgA autoimmune response to BP180 (4, 5). Kromminga et al. found that patients with BP had IgG (81%) and IgA (65%) autoantibodies against NC16a, and that LAD also had IgG (32%) and IgA (16%) autoantibodies against this domain (18).

There are two subsets of IgA antibodies in the LAD. One of them, LAD-1 antigen, is a cleaved 120-KDa ectodomain of BP 180 with a unique epitope for IgA, bound to BP230 and the full-length form BP180 (5). Additionally, in the lamina lucida-type LAD, IgA binds to the roof of the salt-split skin (epidermal side, as with BP) (5, 14). This indicates a relationship between BP and LAD. This relationship could be explained by the "epitope spreading phenomenon" (19). In this phenomenon, the primary disease, such as ordinary BP, exposes the BMZ to the immune system, which produces autoantibodies against BMZ proteins without pathogenicity (4). In our case, IIF using salt-split skin showed IgA anti-BMZ antibodies reactive with the epidermal side.

LAD is actually the most common autoimmune blistering disorder in children. Childhood bullous diseases should be distinguished from other acquired bullous disorders seen in children, such as bullous impetigo, herpes simplex, scabies, arthropod bites, parasitic infections, drug eruptions, dermatitis herpetiformis, and erythema multiforme (1, 2, 4). All were excluded for our patient.

The prognosis of childhood BP is usually good. Cases treated early often respond rapidly to systemic corticosteroids and require treatment for only a period of months. Relapse after stopping corticosteroid treatment is uncommon. For those requiring longer treatment, steroid-sparing agents have been used. In the literature, the drugs used in the treatment of infantile BP are local steroids, rituximab, IVIG, azathioprine, cyclosporine, dapsone, and mycophenolate mofetil. IgA dermatosis appears clinically more severe because of the mucosal involvement. However, its response to steroid treatment is good. Nevertheless, BP may require more aggressive treatment (1–4, 13, 20).

In conclusion, because of the epitope spreading phenomenon, BP and LAD may overlap in infantile patients with mucosal involvement. For the differential diagnosis, various immunological techniques are useful in patients with deep and generalized mucosal involvement, such as our patient. This is especially important for determining the prognosis and expected response to treatment.

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