Neonatal pemphigus vulgaris: IgG4 autoantibodies to desmoglein 3 induce skin blisters in newborns

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Pemphigus vulgaris (PV) is an immune-mediated, bullous skin disease, typically affecting mucous membranes. It is characterized by intraepidermal acantholysis and IgG autoantibodies to the transmembrane, desmosomal protein, desmoglein (Dsg) 3.[1] PV is a disease predominantly of the third to sixth decades of life and is uncommon in neonates and children. PV in neonates is caused by maternal autoimmune disease with transplacental transmission of IgG antibodies.[2-4] We describe a case of neonatal PV where the autoimmune response could be characterized at the molecular level in both the mother and the neonate.

CASE REPORT

A male newborn was delivered without complications (Apgar score, 9/10/10; birth weight, 3100 g) after an uneventful pregnancy. Physical examination showed skin erosions on the head, shaft of the penis, and right foot (Fig 1). Mucous membranes and the remaining skin were not involved.

Histologic examination of a skin biopsy specimen, taken from the right forefoot 3 days after birth, demonstrated an intraepidermal blister with infiltration of eosinophilic and neutrophilic granulocytes.

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The medical history of the family was revisited. The boy was the first child of nonconsanguine parents. The patient's mother had experienced PV with bullae on her head and trunk, and oral mucous membranes for 5 years. Oral, high-dose corticosteroid treatment resulted in improvement with only occasional new blisters. During pregnancy, the mother received no treatment for her PV, and mucosal erosions had become more extensive.

Indirect immunofluorescence microscopy was performed on a monkey esophagus. We could demonstrate the presence of circulating IgG autoantibodies that bound to the epithelium with an intercellular staining pattern in both the mother and the neonate (titer: 1:160 in both serum samples) (Fig 2). Antibodies to Dsg 1 and 3 were analyzed as described.[5,6] Index values of antibodies to Dsg 3 were 22 in the neonate and 169 in his mother (normal <10). Index values of antibodies to Dsg 1 were negative in both mother and neonate.

In a second step, IgG subclasses of antibodies to Dsg 1 and 3 were characterized. We found, predominantly, autoantibodies of the IgG4 subclass at a level of 2.18 in the neonate and >3.0 in his mother (positive > 0.15). IgG3 antibodies were at negative levels in the neonate (0.11) and slightly increased in his mother (0.25). Antibodies of the IgG1 and IgG2 subclasses were at negative values in both patients (Table I).

Further laboratory and microbiologic examinations of the neonate produced normal findings. The existing bullae healed without complications within 3 weeks and no new blisters occurred.

DISCUSSION

Neonatal PV is the manifestation of an autoimmune disease of the mother resulting from transpla-

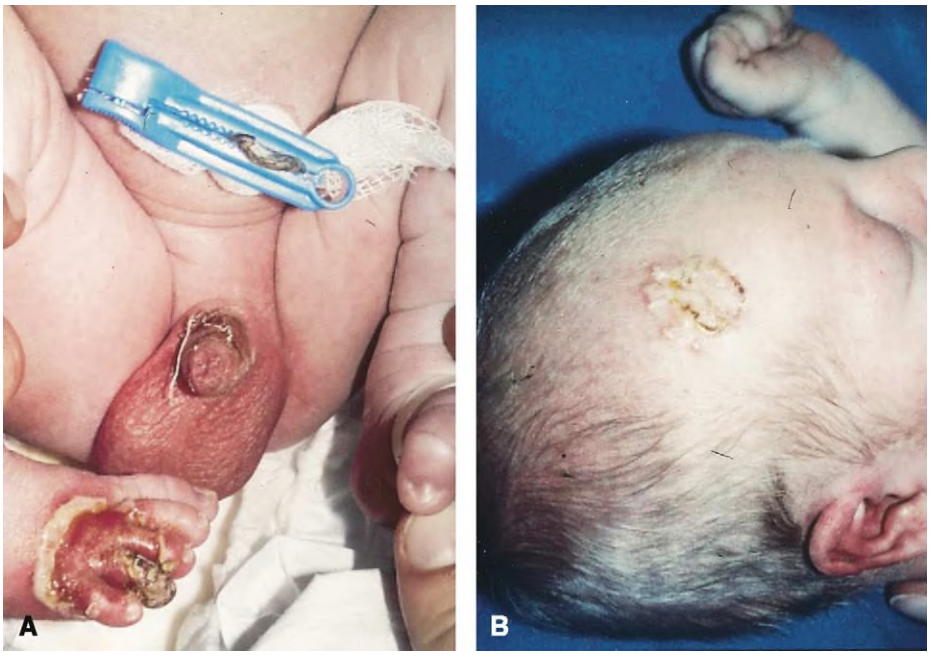

Fig 1. Erosion on penis and right foot (**A**) and vesicles and crusts on head (**B**) on second day of life.

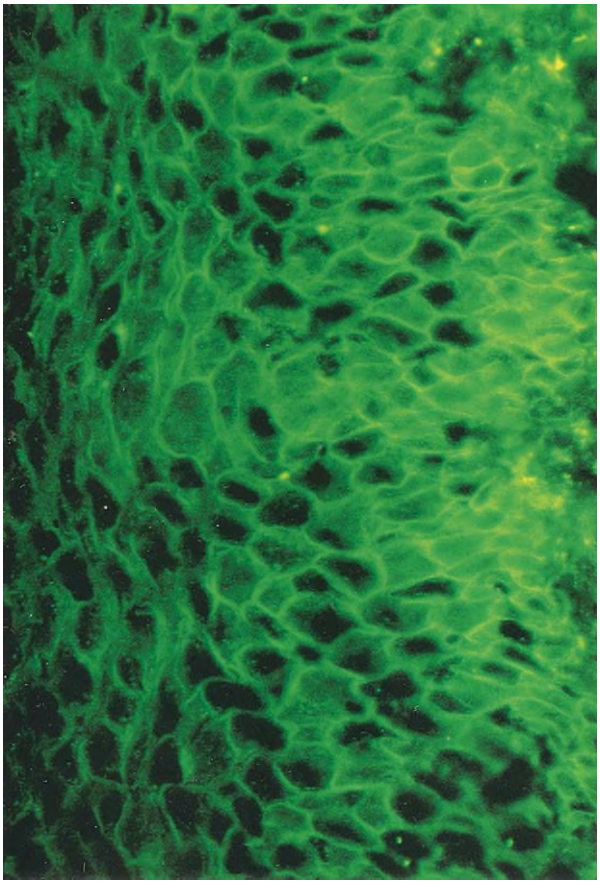

Fig 2. Indirect immunofluorescence microscopy on monkey esophagus (dilution 1:10). Autoantibodies in neonate's serum bind with intercellular pattern to epithelium (original magnification ×400).

cental transmission of IgG autoantibodies, in contrast to idiopathic, juvenile, or childhood PV.[2-4] Neonatal PV has a good prognosis as demonstrated in this child. No medical treatment of the mother was necessary in this case during pregnancy. It is controversial whether therapy with corticosteroids, azathioprine, or plasmapheresis in affected pregnant women is of benefit to the neonate.[7]

In this patient, the autoimmune response of the neonate and his mother could be characterized at the molecular level. Increased antibodies to Dsg 3, but not to Dsg 1, were found in the serum of mother and child. In our opinion, the minor increase of IgG3 levels to Dsg 1 is a result of nonspecific enzyme linked immunosorbent-assay reactivity. As described, indirect immunofluorescence on a monkey esophagus did not show IgG3 reactivity. In addition, enzyme-linked immunosorbent assay with recombinant Dsg 1 did not lead to any polyclonal reactivity against this protein.

In adults with PV, autoantibodies to Dsg 3 lead to mucosal blistering, whereas blistering of the skin is usually caused by autoantibodies to Dsg 1.[1] This is in line with the findings in the mother revealing lesions on oral, mucous membranes and autoantibodies only to Dsg 3. As demonstrated in an animal model, the pattern of expression of Dsg 3 in mucous membranes of adults resembles the pattern found in the skin of neonates.[8] This may account for our

Table I. Subclass reactivity of autoantibodies to desmoglein 1 and 3 in the serum of the neonate and the mother

	IgG1	IgG2	IgG3	IgG4
Anti-Dsg 1				
Neonate	0	0	0.59	0
Mother	0	0	0.66	0.12
Anti-Dsg 3				
Neonate	0	0	0.11	2.18
Mother	0	0	0.25	>3.0

Dsg, Desmoglein.
Numbers indicate readings of optical density; readings >0.15 are considered positive.

finding that antibodies to Dsg 3 caused skin lesions in the neonate.

In addition, we could demonstrate that the neonate's antibodies to Dsg 3 predominantly belonged to the IgG4 subclass. Similarly, it has previously been described that antibodies to Dsg 1 in neonates from mothers with pemphigus foliaceus belong primarily to the IgG4 subtype.[9]

To our knowledge, this is the first case of neonatal PV in which the autoimmune response was characterized at the molecular level. It illustrates the blister-inducing capacity of anti-Dsg 3 antibodies of the IgG4 subclass. Our clinical findings confirm recent experimental data, derived from animal studies, that in contrast to the skin of adults, antibodies to Dsg 3 may induce blisters in the skin of neonates.[9] Further studies will have to investigate at what age the neonatal pattern of Dsg expression switches into the pattern encountered in adulthood.

We dedicate this article to Dr Axel Fenner, Professor of Neonatology and former director of the Department of Neonatology at the University of Luebeck.

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