Herpes Gestationis in a Mother and Newborn

Immunoclinical Perspectives Based on a Weekly Follow-up of the Enzyme-Linked Immunosorbent Assay Index of a Bullous Pemphigoid Antigen Noncollagenous Domain

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Background: Herpes gestationis (HG) is a rare, autoimmune, bullous disease that occurs during the second or third trimester and usually resolves over weeks or months after delivery. Neonates with HG are rare (estimated at 1 per 100,000 cases). Although anti-180-kDa bullous pemphigoid (BP180) autoantibody and transfer of this autoantibody are known as the cause, to our knowledge, no coordinated analysis of clinical symptoms and anti-BP180 antibody enzyme-linked immunosorbent assay titers has been reported in a mother and neonate with HG.

Observations: We describe a 33-year-old woman with HG and her neonate with vesicular erythematous lesions and the weekly follow-up results of the BP180 noncollagenous domain (NC16a) enzyme-linked immunosorbent assay.

Conclusions: Almost the same titer of pathogenic antibody as that in the mother is transferred to the neonate. The plasma elimination half-life of anti-BP180 antibody is approximately 15 days in mother and neonate. An abrupt twin peak increase in the BP180 enzyme-linked immunosorbent assay index from maternal serum was observed just before and after delivery, possibly explaining why HG usually occurs in the last trimester of pregnancy and exacerbates postpartum. Lesions in the neonate resolve without treatment far before pathogenic antibody disappears, suggesting that factors other than anti-BP180 antibodies may be involved in the generation of eruptions. Frequent testing of the BP180 enzyme-linked immunosorbent assay greatly facilitates therapeutic planning.

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HERPES GESTATIONIS (HG), also known as pemphigoid gestationis, is a rare, autoimmune, bullous disease that occurs during the second or third trimester, but it has been reported in the first trimester.1 It flares at delivery and usually resolves spontaneously over weeks or months after delivery. Herpes gestationis is clinically characterized by pruritic urticarial papules or plaques, polymorphous eruptions, and annular or figured erythematous-edematous lesions evolving into vesicles and tense blisters. These skin eruptions usually start on the abdomen and spread over the whole body, including the extremities; the face, scalp, and mucous membranes are much less involved.2,3 Immunologically, HG is characterized by linear deposition of C3 with or without associated IgG at the basement membrane zone on direct immunofluorescence4,5 and by the presence on serum of antibodies to the 180-kDa bullous pemphigoid (BP) antigen (BP180), which is type 17 collagen contained in the hemidesmosomal components.6,7 Epitope mapping has revealed that HG and BP autoantibodies primarily bind at a common antigenic site within the noncollagenous domain (NC16a) of BP180.8 Most HG serum samples are positive for the NC16a domain on immunoblot analysis (93%), with enzyme-linked immunosorbent assay (ELISA) (88%) using the BP180 NC16a domain as the antigen.9

We describe herein a mother and neonate with HG, with precise weekly follow-up studies of the BP180 noncollagenous domain (NC16a) enzyme-linked immunosorbent assay. The present case displayed BP180 ELISA titers in the umbilical artery and vein of 1224.5 and 1021.6, respectively, compared with 1521.8 in maternal venous blood; the plasma elimination half-life of BP180 antibody was approximately 15 days during the first 33 days after birth in the mother and neonate. The BP180 ELISA activity had been eliminated by day 112 after delivery in the neonate, but the maternal level remained higher than normal (at 44.3) as of 19 months after delivery. We present an immunoclinical perspective of HG based on BP180 ELISA analysis of the present case.
A 33-year-old woman with a 1-week history of itchy exudative or urticarial erythema in a figurate and annular pattern, with tense vesicles on the abdomen, presented in gestational week 18 of her third pregnancy (Figure 1A). Examination of the skin revealed palmar plantar pruritic dyshidrosis-like vesicles (Figure 1B). Her medical history included a presumptive diagnosis of pruritic urticarial papules and plaques of pregnancy in the first pregnancy, with delivery of a healthy neonate, and a spontaneous abortion with pruritic urticarial papules and plaques of pregnancy in her second pregnancy. No other history of diseases was elicited. Because severe itching and extension of lesions to the entire body were identified, the patient was admitted to Gifu University Hospital, Gifu City, for corticosteroid treatment. The otherwise healthy newborn boy, weighing 2264 g, had developed annular erythema, with vesicles ranging from coin to walnut size and appearing when he was 3 days old, involving the face, trunk, and extremities (Figure 2A and B). The neonate also developed dyshidrosis-like vesicles on the soles, as did the mother (Figure 2C). These lesions resolved in the neonate by the time he was 10 days old, without treatment. A previous study10 of HG revealed that HLA-DR3 and HLA-DR4 are 2 predominant histocompatibility complex II molecules that are common to patients with HG. In our case, the mother and neonate shared a common HLA-DR antigen, because the mother expressed DR4/15 and the neonate expressed DR4.

Skin biopsy specimens were obtained from the edge of erythema with vesicles on the arm of the mother. A histopathological examination using hematoxylin-eosin staining demonstrated marked subepidermal edema and blisters, with an inflammatory infiltrate mainly comprising eosinophils in blisters and the upper dermis (Figure 3A). Direct immunofluorescence of the skin biopsy specimens showed linear C3 deposits in the basement membrane zone (Figure 3B), whereas IgG was weakly positive and IgA and IgM were not detected.

The BP180 ELISA titers were determined using a BP180 NC16a ELISA kit (MBL, Nagoya, Japan). Briefly, each well
of standard 96-well microtiter plates was coated with recombinant glutathione S-transferase NC16a or the same amount of recombinant glutathione S-transferase. Serum samples, diluted 101-fold, 16 times 101-fold, or 64 times 101-fold, were incubated in duplicate for reaction, and ELISA indexes were determined in accordance with the instructions of the manufacturer.

The mother was initially treated with 30 mg/d (0.6 mg/kg per day) of prednisolone for the first 2 weeks, when the BP180 ELISA index was 2500. By approximately 3 weeks after the initiation of treatment with oral prednisolone at this dosage, eruptions had resolved despite 1 occasion of exacerbation and the ELISA index had also increased once to 5950 before decreasing to 2360 (Figure 4). Because eruptions had mostly resolved, the prednisolone dosage was gradually tapered to 20 mg/d over the following 4 weeks, although the ELISA index remained somewhat higher (approximately >2360) than normal, and this dosage was maintained until delivery, because any further decrease in prednisolone dosage led to flares in disease activity. At 1 week after delivery, prednisolone was decreased by 5 mg/d, resulting in severe clinical recurrence with a marked increase in the BP180 ELISA index. Given this severe recurrence of clinical symptoms and the increased ELISA index, the prednisolone dosage was increased to 35 mg/d for 1 week and gradually decreased to 15 mg/d over 5 months. The mother has been clinically in remission with treatment of 15 mg/d of prednisolone and 100 mg/d of azathioprine. The time course of the BP180 ELISA index in the mother revealed that anti-BP180 activity increased dramatically 1 month before and 2 weeks after delivery to maximum indexes of 2955 and 4300, respectively, and gradually decreased with prednisolone treatment to approximately 50 by 9 months after delivery.

The BP180 ELISA indexes in the umbilical artery and vein were 1225 and 1022, respectively, compared with 1522 in maternal venous blood. Furthermore, the plasma elimination half-life of the BP180 antibody in the neonate was approximately 15 days during the initial 33 days after delivery (Figure 5). Anti-BP180 antibody activity in the neonate, as determined by the BP180 ELISA, was completely eliminated by the time the neonate was 112 days old. Eruptions in the neonate resolved even when the titer of pathogenic antibody was still high (BP180 ELISA index, approximately 770), far before the pathogenic antibody titer disappeared. This may suggest that anti-BP180 antibody is insufficient to generate skin lesions.
COMMENT

The present case study of a mother and neonate with HG focused on the follow-up of BP180 ELISA levels, providing several novel insights that may lead to a better understanding of HG. This was an extreme rare opportunity to be able to follow the BP180 ELISA index in a mother and neonate, because most neonates of mothers with HG are born with normal skin and neonates with vesicular lesions are rare (estimated at 1 per 100,000 cases).11,12

Our case clearly proves that vesicular erythematous lesions in the neonate are caused by transplacental passage of pathogenic antibodies against BP180 NC16a, from the mother to the neonate, as shown by the fact that BP180 ELISA indexes in the umbilical artery and vein were 1225 and 1022, respectively, compared with 1522 in maternal venous blood. Interestingly, indexes from the neonate at 1 and 4 days after birth were 1154 and 784, respectively. Also, eruptions in the neonate disappeared by the age of 8 days, much faster than the disappearance of anti-BP180 activity, suggesting that some unknown factors may be involved in the generation of blisters.

The plasma elimination half-life of IgG is thought to be around 14 days in the average human adult. The present neonatal case revealed for the first time, to our knowledge, a plasma elimination half-life for anti-BP180 antibody of approximately 15 days during the first 33 days after birth. The pathway of anti-BP180 antibody elimination from plasma may involve consumption by binding to antigen in patients with BP in addition to physiological degradation of other IgG levels. Antibody bound to BP180, which is expressed over the entire basal cell surface and on hemidesmosomes in the basement membrane zone, is degraded by internalization from the membrane surface into basal cells and by several proteolytic enzymes generated during the inflammation process because of complement activation at the basement membrane zone. However, the present study suggests that the consumption of pathogenic IgG in the basement membrane zone is not substantial, because the 15-day elimination half-life of pathogenic IgG in the first 33 days is approximately the same as the physiological elimination half-life of IgG.

Herpes gestationis occurs during the second or third trimester (mean onset, 21 weeks) or, in some cases, during the first trimester.1 It flares at delivery in 75% of cases.14 In most cases, it regresses spontaneously over weeks or months after delivery. This seems to be associated with anti-BP180 antibody activity, as shown in an abrupt twin peak increase in the BP180 ELISA index from maternal serum just before and after delivery (Figure 4). Exactly why pathogenic antibody increases before and after delivery remains unclear, but the chorionic membrane, which is rich in BP180 antigen, may become labile at this stage of pregnancy and delivery, resulting in the release of antigen into the maternal bloodstream, in turn activating the production of pathogenic antibody.

The elimination rate of pathogenic antibody from the second peak on day 40 (shown as “b” in Figure 4) to the trough level on day 64 after delivery in maternal serum closely parallels that in the neonate (Figure 5), for the baseline BP180 ELISA indexes of the mother (2955) and neonate (1154) normalized to 100%. After postdelivery day 60, pathogenic antibody disappeared from the neonate, whereas antibody in the mother continued to show a mild up-and-down slope (peak “c” in Figure 4) and stayed in the abnormal range, with a BP180 ELISA index of 43.3, suggesting that the disease activity to produce pathogenic antibody remains present, although much less extensive. This suggests a diagnosis of chronic persistent HG or progression to bullous pemphigoid.

Monitoring the ELISA index is useful when corticosteroid tapering is planned after all skin lesions are gone. Even if all the lesions are gone, we may have to think of keeping a minimum dosage of corticosteroids to suppress antibody production to prevent recurrence, when ELISA indexes remain in high titer, as shown in the mother’s case (Figure 4).

In summary, we have presented herein an interesting coordinate analysis of clinical severity and time course of the BP180 ELISA index, demonstrating the following: (1) almost the same titer of pathogenic antibody as that in the mother is transferred to the neonate; (2) the plasma elimination half-life of anti-BP180 antibody is approximately 15 days during the first 33 days after delivery in mother and neonate; (3) an abrupt twin peak increase in the BP180 ELISA index from maternal serum was observed just before and after delivery, possibly explaining why HG usually occurs in the last trimester of pregnancy and exacerbates postpartum; (4) lesions in the neonate resolve far before pathogenic antibody disappears, and without treatment, suggesting that factors other than anti-BP180 antibodies may be involved in the generation of the eruption; and (5) frequently testing the BP180 ELISA index greatly facilitates treatment planning.

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