Online First

Congenital Epidermolysis Bullosa Acquisita

Vertical Transfer of Maternal Autoantibody From Mother to Infant

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Background: Epidermolysis bullosa acquisita (EBA) is a rare, chronic, autoimmune bullous dermatosis that is caused by autoantibodies against the noncollagenous terminus of the α chain of type VII collagen, resulting in decreased anchoring fibrils in the lamina densa. It classically presents with skin fragility and trauma-induced blisters that are particularly extensive over the distal aspect of the extremities and that heal with milia, dyspigmentation, and scarring, similar in presentation to dystrophic epidermolysis bullosa. Disease onset is typically in adulthood, although rare cases of childhood disease occur. To our knowledge, a case involving a neonate with congenital EBA has not yet been reported in the literature. We describe a newborn with transient EBA due to the passive transfer of maternal autoantibodies.

Observations: A 2-day-old girl was evaluated for tense blisters and areas of denuded skin that had been present since birth. Her mother carried the diagnosis of EBA. The results of histopathologic analysis, immunofluorescence studies, and enzyme-linked immunosorbent assay confirmed the diagnosis of neonatal EBA. The patient improved with supportive therapy and has not required systemic intervention.

Conclusions: Autoimmune neonatal bullous skin disease caused by placental transfer of maternal IgG autoantibodies is rare. It has been reported in neonates born to mothers with pemphigus vulgaris, pemphigus foliaceus, and gestational pemphigoid. To our knowledge, congenital EBA has not been previously reported. Vertically acquired congenital autoimmune blistering disorders appear to be self-limited and resolve with supportive therapy, concomitant with the presumed clearance of maternal autoantibodies from the neonate’s circulation.


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REPORT OF A CASE

A 32-year-old gravida 4, para 3 woman delivered a girl who was noted at birth to have tense blisters and areas of denuded skin. The birth history was remarkable for the induction of labor at 36 weeks of gestation due to oligohydramnios and intrauterine growth restriction. The newborn was vigorous and active at delivery, and no intervention was required. The Apgar score was 9 at both 1 and 5 minutes. The progression of the patient’s skin lesions, with the development of new bullae and poor feeding, was noted on day 1 of life. She was transferred to the neonatal intensive care unit, and the dermatology service was consulted.

On physical examination, the patient was well appearing, though small for gestational age. She had multiple superficial and deep erosions on her face, chest, abdomen, and extremities (Figure 1A), with the most prominent involvement on her hands, ankles, and feet (Figure 1B). She also had scattered intact vesicles and bullae. Her lips and right naris revealed vesicles, erosions, and mild crusting. The oral mucosa was clear, and there was mild subungal hemorrhage of the fingernails.

The patient’s mother carried the diagnosis of EBA. At the time of delivery, the mother had multiple superficial skin erosions with
mild crusting, hypopigmentation, hyperpigmentation, and scarring on the bilateral anterior aspect of her shins, the dorsal aspect of her hands, and her feet. Onychodystrophy was present, and there were no intact bullae.

Previous diagnostic evaluation of the mother, which was completed 1 year earlier at another institution, had included skin biopsy, immunofluorescence studies, and enzyme-linked immunosorbent assay (ELISA). Histopathologic evaluation demonstrated fibrosing granulation tissue with an overlying mildly reactive epidermis. Direct immunofluorescence revealed deposition of IgG, IgM, and C3 at the dermoeidermal junction, with no immunoglobulin deposition within the epidermal intercellular space. The results of ELISA assays for IgG BP180 and IgG BP230 antibody levels were normal. An antinuclear antibody level was only slightly elevated at 1:160, with a homogeneous pattern. These clinical, histopathologic, and laboratory findings strongly favored the diagnosis of EBA.

The patient's mother had a history of esophageal strictures and eye involvement and had been treated in the past with immunosuppressive medications, including cyclophosphamide and intermittent oral prednisone therapy, for flares of her disease. She had discontinued immunosuppressive therapy during the first trimester of this pregnancy. Three other children, born before her diagnosis of EBA, were healthy and had no problems with blistering. There was no other family history of a bullous disorder. The results of an evaluation of the mother for underlying associated conditions were reportedly normal.

Given our patient's clinical presentation and her mother's preexisting diagnosis, we diagnosed probable neonatal EBA resulting from passive transfer of maternal antibodies. Skin biopsy, immunofluorescence studies, ELISA, and immunoblot analysis were performed for diagnostic confirmation. Histopathologic examination of freshly blistered skin of the left thigh demonstrated a pauci-inflammatory subepidermal blister (Figure 2A). Direct immunofluorescence of perilesional skin revealed linear deposition of IgG1, IgG4, IgM, and C3 on the dermal side of the dermoeidermal junction (Figure 2B). Stains were negative for IgA and fibrinogen, and the intercellular epidermal space was free of deposits.

Progressive dilution of the infant's serum sample from 1:10 to 1:5000 layered on salt-split primate skin and stained with fluorescein-conjugated goat anti–human IgG antibodies showed positive staining of IgG at the dermoeidermal junction involving the dermal side for all dilutions 1:10 to 1:40 (Figure 2C). An ELISA assay (Figure 3) was performed using the C-terminal noncollagenous (NC1) domain of type VII collagen as a substrate and the patient's serum sample dilution at 1:100. Bound autoantibody was detected with an alkaline phosphatase–conjugated goat anti–human IgG antibody. Two normal human samples (NHS1 and NHS2), which were used as a control, showed very low reactivity, with values of less than 0.18 OD (optical density). In contrast to the control samples, our patient's serum sample contained anti–type VII collagen antibodies at levels greater than those in a serum sample from a patient with known EBA (positive control). To further confirm the ELISA results, we performed an immunoblot analysis using recombinant NC1. As shown in Figure 4, the 145-kDa recombinant NC1 protein was recognized by our patient's serum sample and by the positive control sample but not by the 2 negative control samples at a dilution of 1:50.

Given the expected spontaneous taper in our patient's circulating antibody level, we held off administering immunosuppressive therapy and opted for supportive treatments, with careful monitoring of her pain and nutritional status. She did extremely well with me-
ticulous wound care, bacitracin ointment to open areas, petrolatum-impregnated dressings, and gauze bandaging. Her initial feeding was poor, but given the potential for mucosal injury, we recommended against gavage tube placement. She was given intravenous fluids and allowed to feed ad lib with a standard formula and a regular infant nipple. Her pain was well controlled with a regimen of acetaminophen and oral sucrose before dressing changes; she required oral morphine on only 1 occasion. During her 1-week hospitalization, new blister development was rare and her feeding greatly improved.

At 3 weeks of age, her lips and oral and nasal mucosae appeared normal. The dorsal aspect of her hands revealed well-healed erosions and dyschromia, with mild subungual hemorrhage of the thumbnails. There were some persistent superficial erosions, with desquamation at the ankles and feet, but no new blisters were present. At 2 months of age, all erosions were completely healed, with only residual scarring, hyperpigmentation, and hypopigmentation. The areas of previous bullae were now studded with multiple milia (Figure 1C).

Figure 2. The findings of histopathologic examination and immunofluorescence studies of the infant were consistent with epidermolysis bullosa aquisita. A, Paucicellular subepidermal blister (hematoxylin-eosin, original magnification ×20). B, Direct immunofluorescence showing linear deposition of IgG, IgA, IgM, and C3 at the dermoepidermal junction on the dermal side of the blister (hematoxylin-eosin, original magnification ×40). C, Indirect immunofluorescence showing positive staining with IgG at the dermoepidermal junction on the dermal side of the blister at a dilution of 1:40 (hematoxylin-eosin, original magnification ×20).

Figure 3. Enzyme-linked immunosorbent assay. On the y-axis, OD (optical density) correlates with the presence of anti–type VII collagen antibodies; OD was measured by absorbance at 405-nm wavelength. Two normal human serum samples (NHS1 and NHS2) showed very low reactivity. Our patient’s serum sample contained anti–type VII collagen antibodies at levels greater than those in a serum sample from a patient with epidermolysis bullosa acquisita (EBA) (positive control).

Figure 4. Immunoblot analysis using a recombinant C-terminal noncollagenous domain (NC1) of type VII collagen. Patient indicates the neonate described in this article. A known patient with epidermolysis bullosa acquisita (EBA) was used as a positive control, and 2 normal human serum samples (NHS1 and NHS2) were used as negative controls.
Epidermolysis bullosa acquisita is an autoimmune bullous disorder that is caused by circulating IgG autoantibodies directed against the 145-kDa NC1 domain of collagen VII. Woodley et al provided direct evidence that human autoantibodies are pathogenic in EBA when hairless immunocompetent adult mice injected with affinity-purified anti-type VII collagen antibodies from the serum of patients with EBA developed clinical, histologic, immunologic, and ultrastructural parameters that were consistent with EBA. IgG1 and IgG4 are the major antibody subclasses in EBA. The plasma elimination half-life of IgG is approximately 14 days in the average human adult. A 15-day half-life of anti-BP180 IgG has been documented in a neonate with gestational pemphigoid. The eruptions in that neonate disappeared by the age of 8 days, earlier than the expected disappearance of anti-BP180 activity. Our patient did not develop new blisters after approximately day 10 of life.

Clinically, there are 2 phenotypes of EBA. The inflammatory type mimics other bullous diseases, including bullous pemphigoid, linear IgA bullous disease, and cicatrical pemphigoid. Classic-type EBA is more common and phenotypically similar to dystrophic epidermolysis bullosa, with skin fragility, trau-ma-induced blistering, scarring, and milia. The oral and ocular mucosae can variably be involved. Epidermolysis bullosa acquisita is rare, with an estimated incidence of 0.25 per million in Western Europe, and most cases are acquired in adulthood.

Childhood EBA has been reported. Children typically present under the age of 16 years. In contrast to adult disease, childhood disease is more typically inflammatory, has an increased incidence of mucosal involve-ment, shows a better response to treatment, and therefore has a better long-term prognosis. Treatment of children consists of prednisone or dapsone, alone or in combination. Follow-up is limited by the rarity of the condition; however, the long-term prognosis for childhood EBA appears good. Positive treatment response and disease remission are seen within months of the initiation of systemic therapy.

Transient autoimmune neonatal bullous skin disorders are rare. The presumed mechanism of disease is passive transfer of maternal IgG autoantibodies across the placental tissues. Neonates born with transient blistering have been documented in mothers with pemphigus vulgaris. (including those who were clinically asymptomatic at the time of delivery), pemphigus foliaceus, and gestational pemphigoid. Autoimmune bullous diseases can be modulated by pregnancy, presumably secondary to the hormonal influences of estrogen and progesterone, with disease expression during pregnancy or immediately post partum. It has been shown that pathogenic antibody to BP180 increases immediately before and after delivery in patients with gestational pemphigoid, presumably in response to the release of the BP180 antigen from the chorionic membrane. The exact role of hormones in accelerating bulla formation or pathogenic antibody titer is unknown.

To our knowledge, no similar studies have been conducted in pregnant women with EBA. Two patients have been described in the literature, including 1 patient who developed EBA on day 2 post partum, with resolution of blistering at menopause, and 1 patient who had a relapse of her EBA during the first month of gestation, with marked improvement of her skin following termination of the pregnancy.

As far as we know, congenital EBA has not been reported previously, likely because EBA itself is an extremely rare disorder. Experience with neonatal pemphigus has shown that such vertically transmitted autoimmune blistering disease appears to be self-limited and resolves with supportive therapy. After 10 days of age, our patient showed no new blister formation, and all erosions were completely healed by 2 months of age. As this is the first reported case of neonatal EBA (to our knowledge), it is premature to make conclusions regarding long-term prognosis.
a mother and newborn: immunoclinical perspective based on a weekly fol-
low-up of the enzyme-linked immunosorbent assay index of a bullous pemphi-
18. Panku JF, Fidell SR, Hadley J, Zone J, Leiferman K, Vanderhooff S. Neonatal pem-
24. Kubo A, Hashimoto K, Inoue C, Hashimoto T, Yoshihikawa K. Epidermolysis bul-

Notable Notes

Reflections on the Hulk’s Green Skin

One of the most popular comic book superheroes is the Hulk, whose mighty muscular physique is covered by strikingly green skin. Hulk also sports green eyes and greenish hair. Although the Hulk’s verdant appearance was created by Stan Lee and Jack Kirby of Marvel Comics, his green skin does have a historical inspiration. For example, a recent report described a 67-year-old jaundiced woman who developed intense green hyperpigmentation while receiving enteral tube feedings that contained FD&C blue No. 1.1 It was postulated that the blue dye in combination with the yellow jaundice produced a 67-year-old jaundiced woman who developed intense green hyperpigmentation while receiving enteral tube feedings that contained FD&C blue No. 1.1 It was postulated that the blue dye in combination with the yellow jaundice produced the patient’s greenish skin discoloration. Rarely, patients with hyperbilirubinemia may develop green skin changes caused by the cutaneous deposition of biliverdin.2

A more common cause of green pigmentary changes in hair, nails, and skin is exogenous exposure to copper.3 Wearing copper jewelry can sometimes cause a localized greenish discoloration of the underlying skin. Green hair may result from swimming in pool water that contains a high copper level.3 Perhaps the most memorable historical cause of a green skin tini in people was chlorosis, a condition associated with iron deficiency anemia, which was commonly observed during the 16th through the 19th centuries, particularly in young women.4 Chlorosis was called green sickness by the general population. Green sickness appears to have affected several Shakespearean characters, including the beloved Juliet, about whom Romeo declared: “Her vestal livery is but sick and green” (Shakespeare W. Romeo and Juliet. Act 2, scene 2). Nowadays, chlorosis is no longer clinically seen, possibly because of the earlier diagnosis and treatment of iron deficiency disorders, among other factors.4,5

For those readers who enjoy figures of speech, here are 2 quick ways to become green: (1) You can turn green with envy, and (2) If you work your garden well, people will praise you for having a green thumb. In the world of creative imagination, the greenish visage of the Hulk does not stand alone. Other notable green characters include the Jolly Green Giant, with his familiar “Ho, Ho, Ho” greeting, and, of course, the endearing ogre, Shrek, who has starred in 4 movies. But of all these interesting creations, the most incredible is the Hulk, even though he must sometimes share his greenish complexion with those mere mortals of medical history known as our patients.

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