
Transplacental passage of maternal pemphigus foliaceus autoantibodies induces neonatal pemphigus

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The association of maternal pemphigus foliaceus (PF) with neonatal PF is rare and may be secondary to transplacental passage of PF autoantibodies. We describe a 25-year-old patient with PF who was delivered of two consecutive babies, one with classic skin lesions of PF and another that was normal. The neonate with PF was born when the mother had widespread skin disease; the normal newborn was born when the mother was in partial remission. The titers of PF autoantibodies were higher in the mother's serum and the cord serum of the baby with PF than in the mother during partial remission and the unaffected baby. The mother and affected baby had autoantibodies to desmoglein 1. Furthermore, cord blood from the baby with PF induced skin disease when injected into mice. In this case, maternal PF was associated with neonatal PF when the titers of maternal anti-desmoglein 1 autoantibodies were elevated. The cutaneous disease in neonatal PF is due to anti-desmoglein 1 autoantibodies. (J Am Acad Dermatol 2000;43:1130-4.)

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Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are diseases that are characterized by mucocutaneous blisters and pathogenic antidesmosomal autoantibodies as demonstrated by immunofluorescence techniques.¹ Whereas PV is a disease of mucosal squamous epithelium and epidermis, PF is a disease that involves only the epidermis.² The autoantibody response in PV is directed against desmoglein 3 (Dsg3) mixed with autoantibodies against desmoglein 1 (Dsg1) in about 50% of the cases.³ In PF, on the other hand, the autoantibody response is mainly to Dsg1. However, both

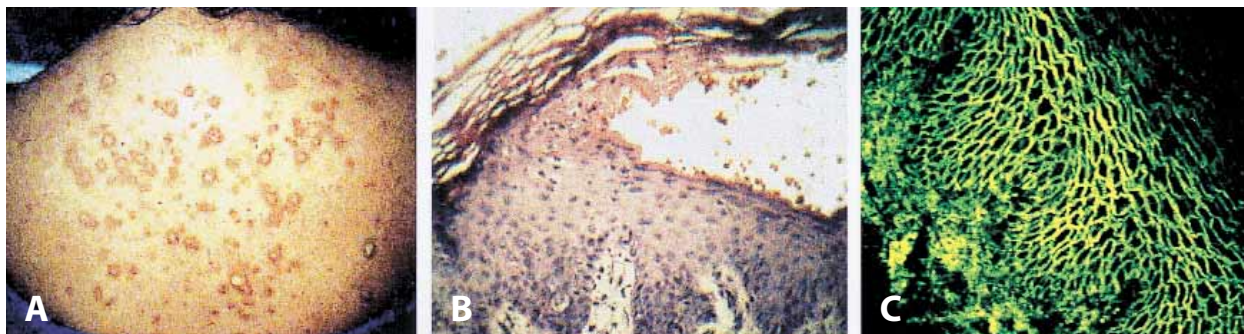


Fig 1. **A**, Mother showed classic PF keratotic plaques on her back. **B**, Skin biopsy specimen from lesional skin showed subcorneal blister. (Hematoxylin-eosin stain; original magnification $\times 400$.) **C**, IIF demonstrated markedly positive staining of IgG in the intercellular spaces on cow nose substrate, at a titer of 1:640.



Fig 2. **A-C**, The first baby with superficial blisters. **D**, Skin biopsy specimen from lesional skin showed a subcorneal blister. (Hematoxylin-eosin stain; original magnification $\times 200$.) **E**, Perilesional skin showed typical intercellular staining with DIF. Baby's cord blood showed titer of 1:160 as tested by IIF.

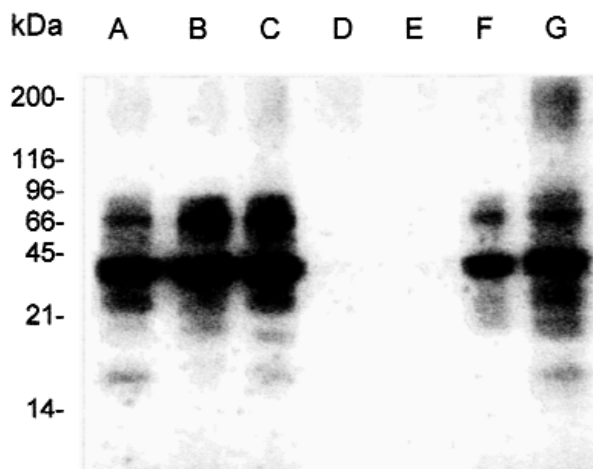


Fig 3. Immunoprecipitation assay of mother and newborn sera using a radiolabeled 45-kd fragment of Dsg1. The serum of the mother (first trimester of the first pregnancy [A]; just before delivery of the baby with PF [B]; and before delivery of the second normal child [G]). Cord serum from the baby with PF is shown in C. Control samples include colostrum (D), amniotic fluid (E), and a serum from a patient with endemic PF (F). Additional bands correspond to degradation products. Molecular weight markers are shown on the left.

anti-Dsg3 and anti-Dsg1 autoantibodies present in the sera of patients with PV or PF are pathogenic.^{4,6} We and others have reported that a predominantly mucosal PV is associated with anti-Dsg3 autoantibodies and a combined mucocutaneous PV with anti-Dsg3 and anti-Dsg1 autoantibodies.^{6,7}

Neonatal pemphigus with classic acantholysis and antiepidermal autoantibodies has been previously described in cases in which the mother of the newborn had active PV.⁸⁻¹² The disease in the neonates was transient and thought to be triggered by transplacental passage of pathogenic autoantibodies. The occurrence of neonatal PF has been occasionally reported in nonendemic PF¹³ skin disease. However, it was not seen in 19 babies born to mothers with the endemic form of PF (fogo selvagem)¹⁴ or in one case of nonendemic PF.¹⁵ The reasons for these interesting observations remain unclear.

In this investigation we describe a mother with classic PF who had two term pregnancies in the course of her disease. The first ended with the delivery of a baby with neonatal PF when the mother had active PF, and the second ended with the delivery of a normal newborn when the mother's disease was in partial remission on prednisone. The baby with neonatal PF had high titers of anti-Dsg1 autoantibodies in the cord serum and bound to affected epidermis. Moreover, IgG isolated from

the baby's cord blood induced epidermal blisters in neonatal mice when passively transferred to these animals. This study further documents the pathogenic role that antidesmosomal autoantibodies play in the blistering disease seen in neonates of mothers suffering from PF.

CASE REPORT AND METHODS

Case report

A 25-year-old Hispanic woman had a 5-year history of PF, documented by clinical, histologic, and immunofluorescence criteria. She was a permanent resident of Zacatecas, Mexico. The initial dermatologic evaluation of the patient was performed during labor with her first baby boy, when she was 23 years old. She had received no treatment for at least 6 months before her labor. She had a widespread eruption characterized by erosions and verrucous plaques (Fig 1, A). Histologic and direct immunofluorescence (DIF) studies were classic of PF (Fig 1, B and C). Indirect immunofluorescence (IIF) of her serum showed an IgG titer of 1:640. The baby's weight was 3500 g, and he had an Apgar score of 8. He presented with an erythematous eruption on the trunk and scattered vesicles on his trunk, arms, and legs (Fig 2, A, B, and C). The histologic examination of the baby's skin biopsy specimen showed typical subcorneal vesicles (Fig 2, D) and DIF showed staining of the epidermal intercellular spaces with IgG and C3 (Fig 2, E). IIF of cord serum was present at a dilution of 1:160. Interestingly, mother and baby showed IgG1 and IgG4 PF autoantibodies. The skin disease of the mother was controlled with systemic steroids (60 mg/day of prednisone) initially and gradually tapered. The skin disease of the baby cleared spontaneously within 2 weeks after delivery. The mother was kept in partial remission for the next 2 years with low doses of prednisone (15 mg/day). At 25 years of age, she had a second uneventful term pregnancy that ended with the delivery of a healthy baby boy weighing 2800 g with an Apgar score of 9. The mother's skin exhibited a few small verrucous lesions on her trunk at the time of delivery but without evidence of blisters. The newborn had normal skin. The mother's IIF titer was 1:80 and the baby's cord serum was 1:20.

Immunofluorescence and immunoprecipitation techniques

Routine immunofluorescence procedures were carried out following protocols reported earlier.^{16,17} Fluorescein isothiocyanate-labeled anti-human IgG and anti-human C3 were obtained from commercial sources (Kinkegaard & Perry Laboratories, Gaithersburg, Md). The IgG sub-

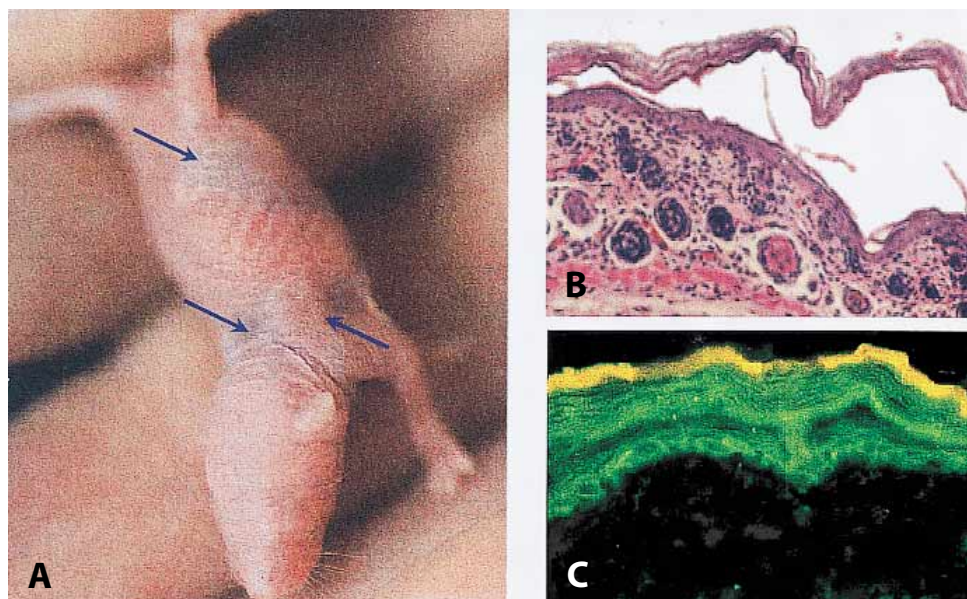


Fig 4. Passive transfer of baby's cord serum IgG into neonatal mice reproduced the clinical (**A**) (arrows in blisters), histologic (**B**) (subcorneal blister), and DIF features of IgG staining of desmosomes (**C**) of human PF.

classes of PF autoantibodies were determined with the use of murine monoclonal antibodies against IgG1, IgG2, IgG3, and IgG4 (Kinkegaard & Perry Laboratories) and fluorescein isothiocyanate-labeled sheep anti-mouse IgG as reported previously.¹⁷ The slides were evaluated with an epifluorescence microscope (Olympus B-Max).

Immunoprecipitation procedures were performed by means of a radiolabeled 45-kd fragment of bovine Dsg1 as described in detail elsewhere.¹⁸ Aliquots of the patient's and babies' sera were incubated with ¹²⁵I-labeled Dsg1 fragment and the immune complexes immobilized with insoluble *Staphylococcus aureus*. The immunoprecipitated ¹²⁵I-Dsg1 was solubilized with 1% sodium dodecyl sulfate and fractionated by 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis. The radiolabeled bands were demonstrated by autoradiography.

Passive transfer into BALB/c mice

The IgG fractions from umbilical cord serum from the two neonates were purified by precipitation with 33% saturated ammonium sulfate followed by diethylaminoethyl cellulose chromatography.^{4,5} This purified IgG was concentrated to 100 mg/mL and filter-sterilized. Approximately 10 mg of IgG per gram of body weight was given intraperitoneally to BALB/c neonatal mice as previously reported.^{4,5} The animals were evaluated clinically, histologically, and by immunofluorescence procedures for several hours after the injections.

RESULTS

Immunoprecipitation assays

The serum samples from the mother obtained during the first trimester of her first pregnancy, during delivery of her first baby, and during her second pregnancy, recognized the 45-kd fragment of ¹²⁵I-Dsg1 antigen (Fig 3, lanes A, B, and G). The upper band at 66 kd corresponded to a nonspecific reaction with albumin, and additional bands were degradation products. The cord serum of the first baby also immunoprecipitated the 45-kd fragment of ¹²⁵I-Dsg1 (Fig 3, lane C). The cord serum from the second baby (data not shown) as well as samples of colostrum and amniotic fluid included as controls did not react with Dsg1 (Fig 3, lanes D and E). The Dsg1 antigenic fragment was also bound by serum from a patient with endemic PF (Fig 3, F) that was included as a control sample.

Passive transfer of umbilical cord IgG

The purified IgG fractions obtained from the umbilical cord of both neonates showed different effects when passively transferred to neonatal mice. The IgG from the umbilical cord of the first baby that showed an IIF titer of 1:160 and immunoprecipitated ¹²⁵I-Dsg1 was able to induce blisters in mice, which showed the typical features of PF histologically and with DIF (Fig 4). The IgG from the second baby that showed negative IIF and immunoprecipitation was harmless to these animals.

DISCUSSION

The present communication describes a young woman with the diagnosis of PF who had two consecutive term pregnancies in the course of her disease. The first ended with the delivery of a baby with clinical, histologic, and immunologic features of PF. The PF of the mother was uncontrolled, exhibiting extensive cutaneous disease and IIF titers of 1:640. The cord serum showed IIF titers of 1:160. Two years later the patient was delivered of her second child. This neonate, however, showed no evidence of skin disease. At this time, the PF of the mother was in partial remission with minimal cutaneous disease and serum titers of 1:80. The cord serum titer of autoantibodies was 1:20. The serum of the mother on both occasions as well as the cord serum of the first baby with PF recognized the 45-kd Dsg1 immunoreactive fragment. On the basis of these findings, we conclude that the mother and the first baby possessed autoantibodies against Dsg1. Furthermore, we demonstrated that the anti-Dsg1 autoantibodies present in the cord serum of the baby with PF were pathogenic when tested by passive transfer experiments. The cord IgG injected intraperitoneally into neonatal mice faithfully reproduced the clinical, histologic, and immunologic features of PF in these animals. These studies strongly suggest that transplacental passage of maternal anti-Dsg1 autoantibodies to the neonate, if present in significant titers in the mother, can trigger cutaneous disease in the newborn. The skin disease in the newborn, in our case, cleared spontaneously.

Our findings are in contrast to those of previous studies.^{14,15} One of these studies was carried out with 19 pairs (mother/baby) in which the mothers had the diagnosis of endemic PF (fogo selvagem).¹⁴ The majority of mothers showed moderately low titers of PF autoantibodies and the babies' cord sera showed low titers or no autoantibodies. Therefore it was concluded that perhaps the placenta was functioning as an "in vivo immunoadsorbent" of pathogenic autoantibodies.¹⁴ It has been suggested that the placenta may modulate the passage of maternal antibodies to the baby by an Fc-receptor-mediated transport mechanism.¹⁹ In the case of anti-Dsg1 autoantibodies, the antibodies may bind desmosomal antigens present in placental desmosomes,²⁰ thereby preventing their transfer to the fetus.

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