

## SHORT COMMUNICATION

## Pemphigoid Gestationis Complicating an Egg Donation Pregnancy

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Pemphigoid gestationis (PG) is a rare autoimmune blistering disease most frequently occurring during the second or third trimester of pregnancy (1, 2). PG manifests either in primiparous or multiparous women, with a tendency to earlier and more severe recurrences in subsequent pregnancies (2, 3). Skin manifestations typically start in the periumbilical area (1), improve before delivery, and worsen again at the time of delivery (4, 5). The major target antigen in PG is the 180-kDa bullous pemphigoid antigen (BP180 or collagen XVII), a transmembrane hemidesmosomal glycoprotein expressed in the basement membrane zone (BMZ) of the skin (1, 5). The expression of BP180 in placental and amniotic epithelia (6) suggests that maternal manifestations of PG may result from cross-reaction between placental and skin antigens.

Microscopically, the presence of a subepidermal bulla with a prominent eosinophilic infiltrate is suggestive of PG (7). Direct immunofluorescence (DIF) microscopy remains the gold standard for diagnosis. Indeed, the diagnostic hallmark of PG is the linear C3 deposition along the BMZ (1). BP180 enzyme-linked immunosorbent assay (ELISA) is a highly sensitive test for PG and may be used to correlate antibody titre with disease severity, even preclinically (1, 8, 9).

We report here a rare case of PG occurring in a woman whose pregnancy was achieved using egg donation (ED), hence carrying a foetus with an entirely allogenic genome.

## CASE REPORT

A 38-year-old woman in her 36<sup>th</sup> gestational week was admitted to our hospital for the acute onset of an itchy urticarial eruption in the periumbilical region, which was followed by blisters that spread to the trunk and extremities in a few days. Physical examination re-

vealed erythematous urticarial-like plaques encircling the navel and scattered on the abdomen, associated with vesicles and bullae (Fig. 1a). Numerous lesions were also present on the buttocks and feet (Fig. 1b). Mucosae were not involved.

The patient had infertility due to primary ovarian insufficiency, and pregnancy had been achieved through *in vitro* fertilization of a donor egg by her husband's sperm, followed by embryo transfer.

A previous uncomplicated pregnancy had been achieved 3 years earlier, using the same assisted reproduction treatment, the only difference being the oocyte donor.

Before both pregnancies, the patient had been treated with oral estrogen therapy to induce regular menses. In the first trimester of each pregnancy oral hormonal therapy had been shifted to local progestin therapy, which was interrupted thereafter. The patient did not report any other previous dermatosis and her past medical history was unremarkable. Complete blood count, conventional biochemical tests and urine analysis were all within normal limits.

Histopathological examination of an erythematous plaque on the trunk showed a hyperplastic epidermis and a dermal, predominantly perivascular, infiltrate of lymphocytes with rare eosinophils. DIF microscopy of perilesional skin revealed continuous linear deposits of C3 (Fig. 1c) and immunoglobulin G (IgG) along the BMZ. Indirect immunofluorescence microscopy demonstrated binding of IgG from patient serum to the BMZ of normal human skin (Fig. 1d) and staining of the epidermal side of salt-split skin (Fig. 1e). ELISA based on BP180 (MBL, Naka-ku, Nagoya, Japan) resulted positive (48.6 U/ml; normal value <9 U/ml), while ELISA for the 230-kDa bullous pemphigoid antigen (MBL) was negative.

A diagnosis of PG was made and the patient was treated with oral prednisone, 0.5 mg/kg/day, for one week, with rapid improvement of PG lesions. Oral steroid therapy was then tapered. At 38-week gestation, the patient underwent elective caesarean section, giving birth to a 3,400 g male infant without

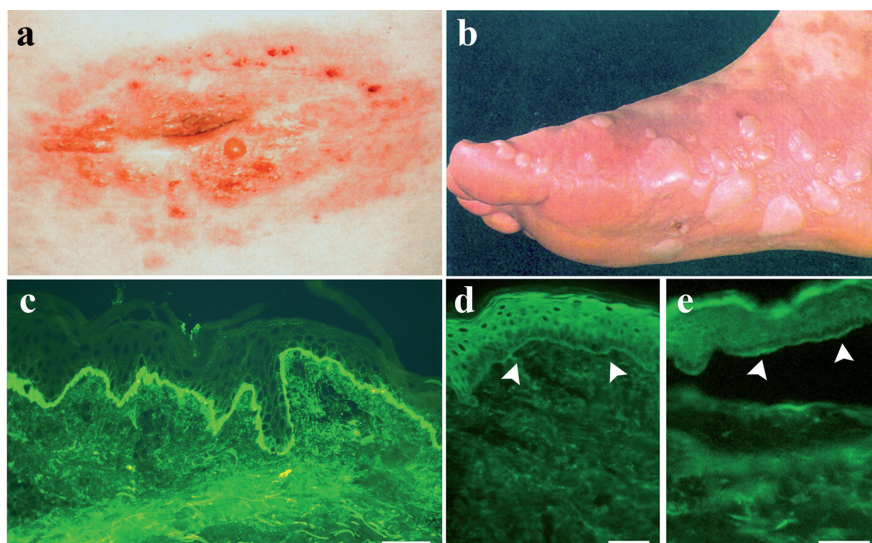


Fig. 1. (a) Periumbilical vesicles and bullae on an erythematous base. (b) Erythema and tense serous blisters on the right foot. (c) Strong C3 linear deposition along the cutaneous basement membrane zone by direct immunofluorescence (IF). (d) Circulating IgG antibodies against the cutaneous basement membrane (arrowheads) detected in the patient serum by indirect IF. (e) Linear staining along the roof of the split (arrowheads) by indirect IF on human salt-split skin. Bars: 50  $\mu$ m (c) and 25  $\mu$ m (d and e). Original magnification  $\times$  20 (c–e).

skin lesions. Fifteen days after delivery, the patient experienced recurrence of PG lesions and prednisone therapy was resumed until complete symptom remission. Since then, the patient has not shown any further relapse of PG.

## DISCUSSION

The case described here is the first report of PG after ED in a multiparous woman who did not show any complication in her previous ED pregnancy. The development of PG in spontaneously conceived (SC) pregnancies has been correlated with maternal major histocompatibility complex (MHC) class II molecules, in particular the human leukocyte antigens (HLA) -DR3 and -DR4 (10). Association with paternal HLA-DR2 has also been reported (10). The improvement in PG symptoms before delivery and the relapse at the time of delivery have also led researchers to link the natural course of PG with progesterone, which has immunosuppressive properties, and with the increase in progesterone levels in late pregnancy, followed by a reduction during delivery (1). However, the exact pathogenetic mechanism of PG remains largely unknown.

In SC pregnancies, placental and foetal tissues have paternal antigens that are foreign to the maternal immune system (1). Thus, the semi-allogenic foetus escapes maternal immune rejection and induces tolerance, creating an immune-privileged site at the foetal-maternal interface (11–13). Nevertheless, silencing of the maternal immune response against an entirely allogenic foetus involves more complex, and possibly different, mechanisms than in SC pregnancies with semi-allogenic foetuses (12). Indeed, ED pregnancies are much more likely to bear a higher degree of HLA mismatches and antigenic dissimilarity between the pregnant women and their children, in comparison with SC pregnancies (Fig. S1<sup>1</sup>) (11, 12). It has been demonstrated that successful ED pregnancies are characterized by an increased number of activated (CD4<sup>+</sup>CD25<sup>dim</sup>) and regulatory (CD4<sup>+</sup>CD25<sup>bright</sup>) T lymphocytes, the latter being implicated in the regulation of the maternal peripheral immune system (13). These findings are combined with a stronger down-regulation of the alloimmune response in the maternal blood of ED compared with SC pregnancies (13). These protective mechanisms could maintain and reinforce the immunosuppressive environment in the pregnant uterus, in this way enabling the entirely allogenic foetus to survive. However, a greater risk for placental complications, in particular pre-eclampsia and gestational hypertension, has been reported in ED pregnancies (12, 14) and suggested to be related to immunological intolerance between the mother and the foetus.

Concerning PG presenting during ED pregnancy, there is only one previous literature report in a primipa-

rous woman (15). It is likely that the increasing use of assisted reproduction technologies, including ED, will lead to an answer to the question as to whether ED can affect the development of PG.

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