

Pregnancy-Triggered Maternal Pemphigus Vulgaris with Persistent Gingival Lesions

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SUMMARY Pregnancy as a triggering factor of pemphigus vulgaris (PV) seems to be quite a rare phenomenon. According to a recent review, only 38 reports describing 49 pregnant women with PV have been published in English language literature. A 34-year-old woman is described with pregnancy-triggered PV showing persistent gingival erosions. In addition, a shift from mucocutaneous to mucosal-dominant clinical variant of the disease in the mother, suggested by clinical features, was confirmed at the molecular level by determination of anti-desmoglein (DSG) 1 and anti-DSG 3 circulating IgG autoantibodies with ELISA. The case presented shows that PV in pregnancy requires care by a gynecologist, dermatologist and neonatologist. They all should be aware of the peculiarities of PV in pregnancy and be willing to cooperate with each other. Noteworthy, in contrast to cutaneous lesions, gingival lesions seen in the mother in the mucosal-dominant stage of her PV after delivery were unresponsive to intravenous and oral corticosteroid/oral cyclophosphamide treatment scheme.

KEY WORDS: pemphigus vulgaris, pregnancy

INTRODUCTION

Pregnancy as a triggering factor of pemphigus vulgaris (PV) seems to be quite a rare phenomenon. Ruach *et al.* (1) found only 23 PV cases in pregnancy published in the literature until 1995, and Fainaru *et al.* (2) 26 such cases until 2000. A recent by Kardos *et al.* (3) appeared in 2009. They found only 38 reports describing 49 pregnant women with PV in the English language literature, including 33 patients with active disease, seven disease free patients, and another nine patients with an unknown dermatological status. Five cases of intrauterine death were confirmed due to umbilical cord prolapse, placental dysfunction, cytomegalovirus pneumonitis, or not diagnosed. Twenty (45%) neonates had pemphigus lesions at birth, while another 24 (56%) were free from lesions. In all 20 children observed, pemphigus lesions resolved within 1

to 4 weeks, either spontaneously or with mild topical corticosteroid treatment (3). Out of all reported cases of neonatal pemphigus, only three were diagnosed as neonatal pemphigus foliaceus (4-6).

We describe a woman with pregnancy-triggered PV showing persistent gingival erosions. In addition, a shift from mucocutaneous to mucosal-dominant clinical variant of the disease in the mother, suggested by clinical features, was confirmed at the molecular level by determination of anti-DSG 1 and anti-DSG 3 circulating antibodies.

CASE REPORT

A 34-year-old woman was referred by her dermatologist to Wrocław Department of Dermatology

for suspected PV. On admission, vesicles with well-strained but relatively frail roof that was interrupted at many sites, thus leading to erosions were present on the skin of the trunk, upper limbs and face (Fig. 1). The total area of skin changes was approximately 100 cm². In addition, erosions were present on the mucous membranes of the mouth and the vermillion border of the lips, occupying approximately 50% of their surface, causing considerable pain and making food intake difficult (Fig. 2).

The onset of illness occurred in December 2008, when the first erosions appeared in the mouth. At that time, she was in the 5th month of pregnancy. The expected delivery date was scheduled for March 2009. The area of erosions in the mouth increased in January and February 2009 and the first blisters on the skin in the region between the breasts appeared in mid March 2009. Cesarean section was performed on March 26, 2009. The birth was on time (gravida 2, 38/39 weeks of pregnancy, male newborn, birth weight 3550 g, birth length 53 cm, Apgar score 10). Approximately 50% of his body surface was covered with diffuse infiltrated erythema, with blisters with frail roof leading to erosions on this base. Consultant dermatologist suspected the following diseases in the mother: herpes gestationis, erythema multiforme or PV, and impetigo neonatorum in the newborn. The patient's serum (only mother's) was referred to Laboratory of Immunology, Poznan Department of Dermatology for pemphigus antibody tests. IgG antibodies against DSG 3 were revealed by ELISA (MBL reagents, Japan) at the level above 150 AU/mL and against DSG 1 at the level 82.20 AU/mL (cut-off points were set at 40 AU/mL and 41 AU/mL, respectively, based on the analysis of ROC curves obtained in this laboratory). In addition, the presence of IgG antibodies against intercellular spaces of the epithelium of monkey



Figure 1. Vesicles with frail roof on the infiltrated erythema background present on the face.



Figure 2. Desquamative gingivitis as an initial clinical feature.

esophagus (Euroimmune reagents, Germany) was demonstrated at a titer 1:640 by indirect immunofluorescence test (IIF). The child remained under the care of neonatologists at the hospital for 14 days after birth. During this time, the skin lesions completely disappeared. Unfortunately, the child's serum was not tested for the presence of pemphigus antibodies. The mother, in whom dermatologist suspected PV, was discharged from the hospital; only subsequent dermatologic consultation was recommended.

Just one week after delivery, she developed a number of blisters on the back and upper extremities, so the patient was referred to Wroclaw Department of Dermatology. Skin biopsy was obtained for direct immunofluorescence test (DIF) and histologic examination. The presence of IgG and C3c deposits in the intercellular spaces of the epidermis was demonstrated on DIF. There were no IgA, IgM and C1q deposits (DAKO reagents, Denmark). The histological preparation stained with hematoxylin-eosin revealed suprabasilar separation with numerous acantholytic cells (Fig. 3). Changes in the epidermis were accompanied by infiltration of inflammatory cells, mainly focused around hair follicles. In addition, the presence of IgG antibodies against intercellular spaces of the epithelium of monkey esophagus (Euroimmune reagents, Germany) were demonstrated by IIF. Clinical and histologic features as well as the results of DIF and IIF were the basis for diagnosing PV. At that time, the results of laboratory testing done in Poznan reached the Wroclaw Department supporting the diagnosis. In addition, the following parameters exceeding normal range were recorded: elevated levels of D-dimer (2710 ng/mL, normal range: 70-490 ng/mL) and antithrombin III (125%, normal range: 85%-115%) and low concentration of albumin (2.8 mg%, normal range: 3.8-5.4 mg%). Leukocytosis (14960/mm³) was

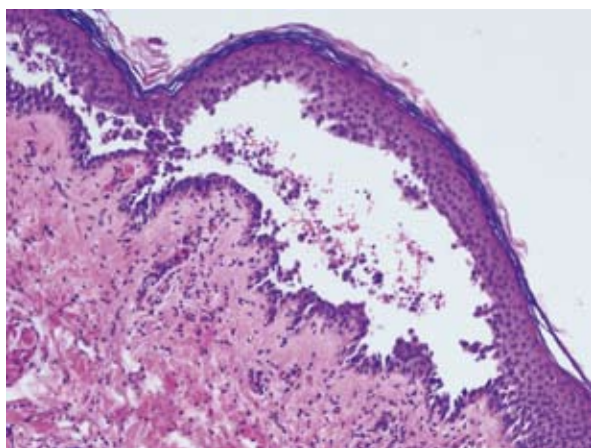


Figure 3. Histologic preparation from biopsy from the mother's back revealed suprabasilar separation with numerous acantholytic cells. (hematoxylin-eosin stain; original magnification: x200)

recorded after steroid administration, but was within the normal range before. Other routine tests were within the normal ranges. The treatment was started with the infusion of methylprednisolone hemisuccinate (a single dose 500 mg iv) and as continuation oral therapy included prednisone 60 mg/d and cyclophosphamide 100 mg/d introduced on April 10, 2009. On May 21, 2009, the patient was re-hospitalized for follow-up, primarily for monitoring treatment adverse events and to administer the next 500 mg methylprednisolone hemisuccinate iv infusion; oral therapy was continued, but at a dose of prednisone reduced to 50 mg/d. Clinically, substantial improvement of the skin changes was achieved. There were no new lesions on the skin from her last stay at the Department, and initial lesions were now covered with crusts. Nevertheless, extensive erosions were still present on the mucous membranes of the mouth. Her next stay at Wroclaw Department took place in July 2009. On admission, there was only post-inflammatory discoloration, no erosions or crusts were present. Improvement was also seen in oral mucosa and the area of erosions occupied about 10% of the surface. Consultant gynecologist did not find any pathology. Significantly, the scar after the cesarean section had healed completely and was free from any skin lesions. During this hospitalization, the third dose of methylprednisolone hemisuccinate (a single dose 500 mg iv) was administered and oral therapy continued. The level of leukocytes and other laboratory parameters were in the normal ranges. The doses of drugs were reduced: prednisone to 40mg/d and cyclophosphamide to 50mg/d. On the next outpatient visit on August 25, 2009, there were no skin changes, only mu-

cosal lesions were seen. Prednisone was reduced to 25mg/d and the treatment with cyclophosphamide was finished. In September, the patient resumed her professional work. The patient reduced prednisone to the dose of 5 mg/d. The next outpatient visit was in November 2009. Still, no active skin changes were seen, only post-inflammatory discoloration remained. There were only gingival erosions occupying a few percent of the mucous membranes. Serum was obtained for immunologic tests. IgG antibodies against DSG 3 were revealed by ELISA (MBL reagents, Japan) at the level of 135.69 AU/mL (cut-off point, 40 AU/mL) and against DSG 1 at the level of 2.84 AU/mL (cut-off point, 41 AU/mL), indicating the presence of persistently active mucosal-dominant PV. The patient confirmed that her child (8-month-old boy) was completely healthy. Both his skin and mucous membranes were free from any changes after discharge from the neonatal ward. Again, the child's serum was not tested by DSG 3/1 ELISA.

DISCUSSION

In our case, the apparently neonatal PV (as suggested clinically) resolved spontaneously during the first two weeks, as in all other reported cases of neonates born with only limited changes that disappeared in the first 2-4 weeks of life (3,7-10). As far as PV in pregnant women is concerned, intrauterine death is the main cause of the aggregate perinatal mortality rate, estimated by Kardos *et al.* (3) at about 12%. Therefore, it seems that neonatal pemphigus is not dangerous for a child born with healthy skin or with only limited changes. The most important observation is that these changes resolve spontaneously or only topical steroids are required (3,7-10). In our opinion, the neonates should be cared for at neonatal ward until skin lesions completely disappear. Hospitalization offers an opportunity for careful monitoring of skin changes and other clinical and laboratory parameters, preferably including the level of autoantibodies to desmogleins (8).

We believe that the cesarean section performed in our patient could be a standard procedure, conceivably preventing induction of pemphigus lesions such as blisters or erosions in genital region during parturition; however, there are only scarce data on this aspect in other reports to support our feeling (11). Our patient was free from any lesions in this region. On the other hand, some authors suggest vaginal delivery because it is more natural, and PV and corticosteroid therapy may complicate wound healing after cesarean section (2), but no complications were observed in the four cases treated by Kalayciyan *et al.* (11).

There are some case reports on similar cases, i.e. a mother with limited, only oral PV and transient,

extensive skin lesions in the child (10,12,13). This clinical phenomenon may occur and could be explained because the pattern of DSG distribution in neonatal skin is similar to adult mucosal epithelia (12). This clinical observation offers additional confirmation to the DSG compensation theory (12,14,15). With this theory, it is easy to understand why only three cases of neonatal pemphigus foliaceus have been reported (4-6). A study carried out by Rocha-Alvarez *et al.* (16) provides further evidence. Nineteen neonates delivered by mothers with active fogo selvagem, an endemic pemphigus foliaceus, were enrolled. All neonates had completely healthy skin despite the fact that pemphigus autoantibodies in low titers were present in the sera of nine neonates and in five children DIF revealed IgG deposits in the intercellular spaces of the epidermis.

Our patient underwent a shift from initially mucosal-dominant PV to mucocutaneous PV, and reversion to the mucosal-dominant form again, and this reversion was confirmed by ELISA results. Our clinical observation and results of evaluating anti-DSG antibody levels were consistent with the DSG compensation theory (12,17).

Pregnancy was recognized as a trigger of pemphigus (12,13,18), or only a factor of exacerbation (8,19-21). Our case belonged to the former category. Cases of a child conceived during active PV period (2,22) and of neonatal PV in children born to women in remission (23,24), or in pre-pemphigus stage, without clinical features but only with the presence of autoantibodies against DSG 1 and 3 (25) have also been described. Pemphigus in the mothers was usually exacerbated. These cases should sensitize doctors and patients alike to the need of proper contraception. It should be emphasized that in some of such cases, even a decision to perform therapeutic abortion was made (18,21).

A pregnant woman with PV was treated successfully with a combination of systemic corticosteroids and plasmapheresis (26). This therapy seems to be the therapy of choice. Our patient was not diagnosed before childbirth, so, unfortunately, she was not treated until the first week after delivery, when severe skin changes appeared and at last the patient was admitted to department of dermatology. We used systemic corticosteroids with cyclophosphamide, with good results. Pemphigus vulgaris clinically manifested solely as erosive lesions of mucous membrane may remain undiagnosed for a long time, as in our case. Desquamative gingivitis, a feature observed in our patient in the beginning and still persisting, could be an isolated symptom of PV (27,28). A similar case has been described by Endo *et al.* (17). They observed

disease progression from mucosal to mucocutaneous involvement in a patient with desquamative gingivitis associated with PV (17). Importantly, erosions, untreated or treated improperly, of oral mucosa cause impairment in food intake, which can hamper fetal development. A low albumin concentration, as in our case, can indicate inadequate diet. Thus, a pregnant woman with erosions of oral mucosa should consult a dermatologist to make an accurate diagnosis and to introduce appropriate treatment as early as possible (13). Elevated plasma fibrin D-dimer and antithrombin III were interpreted as a consequence of cesarean section (29). Marzano *et al.* (30) showed that patients with active PV had the levels of coagulation markers within normal ranges.

Our patient was aged 34 and PV features appeared 3 months before childbirth, i.e. in the sixth month of pregnancy. According to literature data, the mothers to neonatal pemphigus children were aged (years) 25 (5), 27 (18), 28 (9,19), 30, 31 (11), 32 (8,11), 33 (11), 36 (7), 42 (20), and the oldest mother was aged 46 (21). It seems that the range of maternal age, i.e. the youngest 25-year-old and the oldest 46-year-old, is not specific, so we assume that the age of pregnant women is not relevant for triggering PV.

CONCLUSION

Our case indicates that PV in pregnancy requires care by a gynecologist, dermatologist and neonatologist. They all should be aware of the peculiarities of PV in pregnancy and be willing to cooperate with each other. Moreover, as the gingival lesions seen in the mother in the mucosal-dominant stage of PV after delivery could have suggested clinically not just PV, but above all mucous membrane pemphigoid, it was necessary to perform follow up with DSG 3/1 ELISA to confirm that the disease we were dealing with was still PV. In accordance with the concept on the existence of not only intra- but also inter-molecular epitopes spreading/shifting phenomena in autoimmune blistering dermatoses, one also should be aware that the development of such a dermatosis outside pemphigus spectrum is conceivable in an individual diagnosed initially with pemphigus. Finally, our case shows that oral PV lesions can be resistant to traditional treatment modalities. It needs to be determined whether newer treatment options, such as intravenous immunoglobulins and/or rituximab, could be efficacious in such cases.

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