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Pemphigoid gestationis

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AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection · **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** Funds Collection

SUMMARY

A 28-year-old primipara was diagnosed with pemphigoid gestationis, a very rare skin disease, in week 32 of gestation. Thanks to the joint effort of dermatologists and gynecologists, the patient was treated successfully and delivered a full-term healthy child without any symptoms of congenital pemphigus neonatorum.

Key words: pemphigoid gestationis; pregnancy dermatoses; corticosteroids

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INTRODUCTION

Pemphigoid gestationis is a very rare autoimmune blistering skin disease with the prevalence of 1:50,000 to 1:60,000 pregnant, usually white women [1,3]. This disease is mostly related with intense discomfort associated with pruritus and skin condition in the mother, but it can also lead to miscarriage (10–15%), pre-term birth (16–34%), IUGR (34%) and congenital pemphigus neonatorum in the child [1,5].

CASE PRESENTATION

A 28-year old primiparous woman, previously healthy, with a negative family history of autoimmune diseases, was referred to the ward of pregnancy pathology of the Municipal Hospital in Poznań in week 34 of gestation due to pemphigoid gestationis. The first symptoms appeared in week 31 of gestation in the form of intensely itching erythematous skin rash in the region of the umbilicus which later spread to hands, forearms, feet and lower legs (Fig. 1). In week 32 of gestation, the patient was referred by her attending gynecologist to a dermatologist for consultation. At the dermatological clinic, samples of the lesions were taken for direct immunofluorescence (DIF), indirect immunofluorescence (IIF), ELISA and microbiological cultures. These revealed as follows:

- DIF – linear C3 accumulation along the dermoepidermal junction as well as in the basement membrane of the follicular epithelium, with areas of sinusoid arrangement, no IgA, IgM, IgG, IgG1 or IgG4 deposits;
- IIF – no antibodies against desmosomal proteins of the epidermal spinous layer or against IgG and IgG4 basement membrane zone (BMZ) antigens on monkey esophagus substrate;
- ELISA – IgG against BP180 of 78,609 RU/ml (norm to 20 RU/ml), the level of antibodies against BP230 was not increased;
  Culture tests were negative.

Based on the results, pemphigoid gestationis was diagnosed. During hospitalization in the pregnancy pathology ward, oral steroid thera-

py was implemented as ordered by a dermatologist, i.e. 20 mg of prednisone/24h, clobetasol ointment applied to the skin lesions twice daily and cetirizine p.o. once daily, enoxaparin 0.4 sc. and dexamethasone 2x12 mg im. The patient stayed at hospital for 3 days; the fetal state was monitored: US fetal biometry, Doppler UA and MCA, length of the cervical canal pv., CTG, and maternal condition was observed: RR monitoring, glucose and electrolyte levels. US, CTG and laboratory findings were normal. The patient was discharged for further outpatient gynecological treatment. As ordered by a dermatologist, the patient reduced the dose of prednisone to 10 mg/24h after 2 weeks. She was re-admitted to the pregnancy pathology ward in week 37 of gestation. The state of the skin had improved significantly (reduction of the number and severity of lesions) and itching had regressed complete (Fig. 2). Fetal growth was assessed as normal in US. Due to shortened APTT, the dose of enoxaparin was increased to 0.8 s.c. In week 38 of gestation, the patient delivered a healthy full-term girl (2800 g/50 cm), umbilical artery pH 7.37, Ap 10, with no signs of congenital pemphigus neonatorum. Treatment with prednisone at a dose of 10 mg/24h was continued after delivery. The patient was discharged on day 4 after surgery with recommendations of further treatment in the dermatology clinic. The patient was treated with prednisone at a maintenance dose of 5 mg/24h until 12 weeks after delivery. The skin lesions regressed completely (Fig. 3).

DISCUSSION

Pemphigoid gestationis usually develops in multiparous women in the second and third trimesters of gestation, rarely in the first trimester [1]. The disease is said to be associated with a number of other autoimmune diseases, such as Graves' disease (10% of PG patients), pernicious anemia, vitiligo, alopecia areata and immune thrombocytopenia. It can also accompany hydatidiform mole [1,7,9,10].

The disease is associated with the presence of cross reactivity resulting from the formation of IgG antibodies against extracellular non-collagenous NC16A epitope of the BP180 protein (collagen XVII), which can be found in the skin (hemidesmosomal fragment) as well as in

Fig. 1. June 6 2016, week 34 of gestation; prior to prednisone therapy

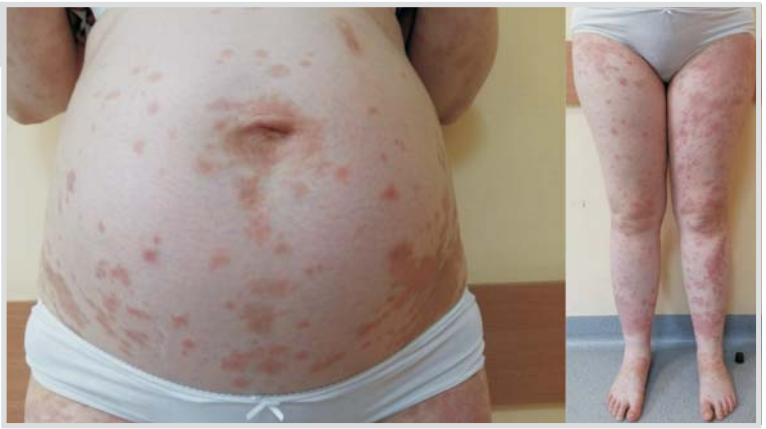
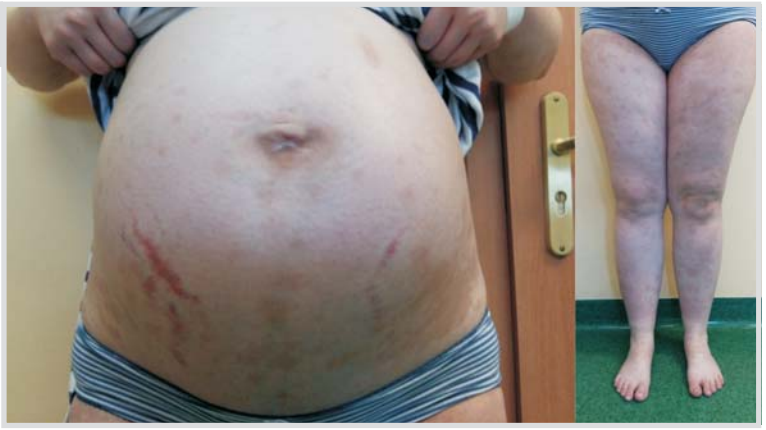


Fig. 2. June 23 2016, week 37 of gestation; after 2 weeks of prednisone therapy



placental and fetal tissues. The presence of IgG antibodies promotes accumulation of C3 complement components in the basement membrane zone, leads to chemotaxis and stimulates eosinophilic degranulation. In consequence, basal keratinocytes adhesion breaks and blisters form [1,7–9]. To date, the factor that causes such a potent immune reaction has not been identified with certainty. The roles of MHC II-class HLA-antigens DR3 and DR4 and sex hormones are underlined [1,3,7–10].

The disease is manifested approximately in week 21–28 of gestation by continuously increasing itching and appearance of papular, patchy, erythematous and finally bullous skin lesions (variable appearance), initially in the area of the umbilicus and later spreading to the extremities. Facial skin and mucus membranes are not involved [3]. Time from the first skin manifestation to the development of blisters varies from several days to 4 weeks. The disease regresses in the final weeks of pregnancy, but exacerbates during labor in 75% of patients [1,3,9].

Histopathological assessment typically reveals epidermal cell edema, subepidermal blisters as well as eosinophilic and lymphocytic infiltrations. DIF of the maternal serum (a diagnostic gold standard) reveals C3 complexes along the basement membrane zone (100% of cases) and possibly linear accumulation of IgG (usually in 25–50% of cases) [1,9]. In IIF, antibodies referred to as *PG factor*, i.e. usually IgG1 or IgG3, are found in the serum in 20% of patients. Their level does not correlate with disease severity [3,5]. The ELISA assay is applied to test the level of antibodies against BP180. Additionally, 10% of patients have positive antibodies against BP230 (intracellular antigen) [1].

The fetal risk is associated with placental insufficiency. Earlier onset and bullous form carry a less favorable prognosis concerning obstetric outcomes, i.e. miscarriage, pre-term birth, IUGR or intrauterine death [5,9]. To date, no guidelines on optimal PG patient monitoring have been developed. Risks can be evaluated by: assessment of fetal growth, flow in the umbilical arteries and biophysical profile. The risk of pre-term birth can be estimated with an assessment of the cervical length in a pelvic examination [4].

To date, no clinical trials to determine optimal pharmacotherapy in PG patients have been conducted [1]. Minor lesions are treated with oral glucocorticosteroids and antihistamines (second generation drugs are preferred due to their lower sedative effects). In severe forms, oral steroids are implemented (usually prednisolone at a dose of 0.5–1.0 mg/kg/24h, starting from 20–40 mg/24h; doses over 60 mg/24h are associated with more frequent IUGR) [5]. Prednisone and prednisolone are recommended since in 88% they do not cross the placenta, by contrast with dexamethasone and betamethasone [12]. The dose is gradually decreased, usually after approximately 2 weeks and as symptoms regress. One should bear in mind the risks associated with GC use during pregnancy: first trimester: risk of cleft palate; second and third trimesters: IUGR, gestational diabetes, pre-eclampsia and pre-term birth [12]. In extremely severe cases, plasmapheresis, immunoglobulin G, cyclosporine, cyclophosphamide, rituximab and goserelin can be added [3]. Pemphigoid gestationis is not an indication for a scheduled cesarean section [4]. The neonatal antibody levels are the same as the maternal ones. This results from their free placental transition. No congenital defects are observed in neonates born of PG mothers; 10% of children [6] have PG-typical skin rash, which regresses within

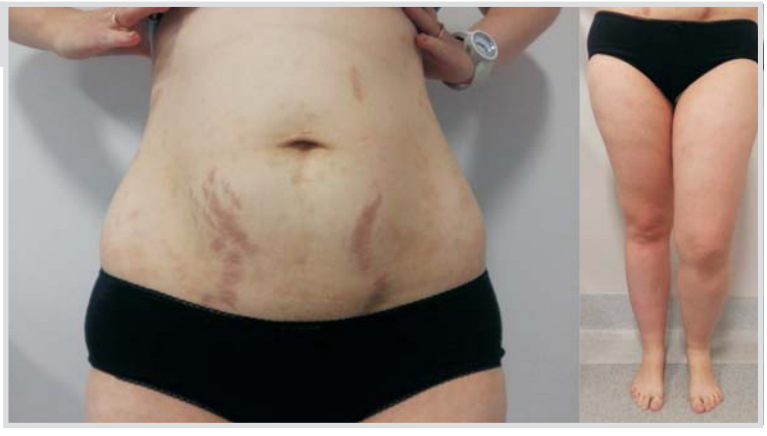


Fig. 3. September 27 2016; 12 weeks after delivery

6 weeks after birth. The skin manifestation reduces faster than antibody levels in neonates. No immunosuppressive therapy is needed. There are no major contraindications to breastfeeding. It is even suggested that it speeds up the involution of lesions (immunosuppressive action of prolactin) [3]. However, the risk of adrenal insufficiency is underlined in children of mothers treated with prednisolone doses >40 mg/24h [1,3]. There are no data on the follow-up of children of PG mothers. PG skin manifestations regress in the mother within 2–6 weeks after delivery. However, they have been reported to persist for a year to even 12 years after delivery [1,2,9]. The risk of recurrence in the next pregnancy is high (faster and much more intense antibody accumulation) and when using hormonal contraception. The disease that does not regress after birth can develop into bullous pemphigoid (approximately 5% of cases) [3].

CONCLUSIONS

Early diagnosis and implementation of immune suppression is of paramount importance for the mother and fetus. Not only does it reduce the risk of *in utero* complications and congenital pemphigus neonatorum, but also improves the comfort of the pregnant and assures that adequate information about her future maternity plans can be given.

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