A severe case of pemphigoid gestationis persisting after labour – case report and review of the literature

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Background and Aim. Pemphigoid gestationis (PG) is a rare skin disease of pregnancy. Given its incidence in pregnant women, physicians and especially obstetricians may not encounter this diagnosis in their entire career. We find this to be a major problem and there is an obligation to report it in as much detail as possible along with recommended treatments with proven efficacy.

Case report. We describe the case of a 27 year old patient who was referred to the dermatology department with severe dissemination of blisters in the 9th week of pregnancy. She was diagnosed with pemphigoid gestationis in her first pregnancy. High doses of corticosteroids were initiated but due to inadequate effect cyclosporine was added. The pregnancy was complicated with gestational diabetes. The patient gave birth in her 33rd week by caesarian section due to premature rupture of the membrane. Vesicles were seen on the newborn immediately after birth which diminished spontaneously over 2 weeks. Blisters were still seen on the patient 1 month after labor even with the combination of systemic corticosteroids with cyclosporine.

Conclusion. PG is a rare dermatosis of pregnancy. The course of the disease can be severe, necessitating systemic therapy. As described in this patient, systemic corticosteroids may not be sufficient and adding another immunosuppressive treatment may be needed. If pemphigoid gestationis has occurred during a previous pregnancy it is advised to reconsider another pregnancy.

Key words: pemphigoid gestationis, herpes gestationis, blisters, pregnancy

Received: October 12, 2022; Revised: February 7, 2023; Accepted: February 17, 2023; Available online: March 14, 2023
https://doi.org/10.5507/bp.2023.010

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INTRODUCTION

Pemphigoid gestationis (PG) is a rare autoimmune disease mostly associated with pregnancy. Pemphigus refers to a blister or pustule and gestationis is the Latin term for "pregnancy-related." PG is a recognized pregnancy associated dermatosis and can be linked to with other pregnancy-related diseases such as the polymorphic eruption of pregnancy (PEP), intrahepatic cholestasis of pregnancy (ICP), and atopic eruption of pregnancy (AEP). Diagnosis of PG is defined by clinical symptoms such as stubborn pruritus and urticarial red raised, itchy bumps and vesicles or plaques which are usually spontaneously healed soon after delivery or termination of pregnancy. PG radically affects the quality of life of pregnant women and can harmfully impact the pregnancy and development of the fetus. Pemphigoid gestationis is estimated to affect approximately 1 in 50 000 to 60 000 pregnancies. The disease is often diagnosed in the second and third trimesters, but can also be identified in the postpartum period[1]. Fetal prognosis is generally good, however PG has been associated with fetal risks such as premature delivery and small for gestational age (SGA). Due to the passive transfer ofantibodies from the mother to the fetus, about 10% of newborns may develop mild urticaria-like or vesicular skin lesions, known as neonatal pemphigoid[2].

According to Shornick et al., only 5% (ref.[1]) of newborns have transient cutaneous involvement. An Italian review analysis published in 2020 demonstrates themain characteristics of pemphigoid gestationis[3]. As reported by the study, the median age at PG onset in mothers was 28, while median gestational age at PG onset was 7 months and median gestational age at delivery was 37 weeks (IQR: 35–39). PG was associated at onset with pregnancy in 85% of PG cases. First-line treatment was initiated during pregnancy in 79.2% of patients and only 13% of newborns suffered with skin lesions. Intrauterine spontaneous fetal death was observed in 5.3% of cases. Limitations of this study (especially regarding the effectiveness of treatment) include the lack of randomized or controlled trials, resulting in the analysis of only case reports and small case series from 1970–2020 (ref.[3]).

Pathophysiology

The basis of the disease is acantholysis of the epidermis, meaning there are many suprabasal blisters. The acantholysis is caused by various autoantibodies, later an immune reaction against epidermal glycoprotein is started. The name of this glycoprotein is desmoglein 3, a protein belonging to the cadherins. Cadherins are calcium binding transmembrane proteins. They are a part of desmosome. The antigen of desmoglein 3 (molecular weight 130 kD) is bound to plakoglobin, also a desmosomal adhesion molecule, (molecular weight 85 kD). Antibody fixation to the extracellular adhesive domain of desmoglein 3 causes damage to the connection between neighboring epidermal cells, causing the formation of the acantholytic cracks. There are three theories of the origin of the disease: effect of plasminogen activator, effect of complement factors, and effect of inflammatory mediators. The etiology is unknown. Initial manifestations may be preceded by UV radiation, X-ray radiation or by burns. Pemphigoid can be also provoced by drugs such as D-penicillamine. Most patients form antibodies against two hemidesmosomal proteins BP180 (also called BPAG1 or collagen XVII) and less frequently BP230. Collagen XVII is a member of the transmembrane collagen family which is a hemidesmosomal component of the dermoepidermal anchoring complex. Collagen XVII is also part of placental tissue, fetal membrane and skin surface. Autoimmune response triggers complement activation and chemoattraction of eosinophil granulocytes followed by degranulation and tissue damage[4]. Dysregulation of collagen XVII may be associated with the development of blistering skin diseases[5]. Ectodomain of collagen XVII is found in epidermis, pemphigoid blisters, and placenta and amniotic fluid[6]. The ectodomain behaves as the PG antigen and is expressed by both syncytial and cytotrophoblastic cells of the human placenta during the first trimester of pregnancy. The collagen XVII ectodomain in amniotic fluid is structurally identical to the ectodomain produced by cultured human keratinocytes[7]. The autoimmune response in pemphigoid diseases has been proposed to be initiated by either the presentation of abnormal MHC molecules of placental collagen XVII or allogeneic reaction of placental stromal cells to collagen XVII presented in the context of paternal MHC molecules[8]. The pathologic mechanism is an autoimmune reaction against collagen XVII in the placenta and, thus, a crossreaction with collagen XVII in the maternal skin base membrane[9]. These specific proteins presented in the placenta are recognized as foreign, causing subsequent production of antiplacental IgG antibodies that cross-react with the same collagen XVII in the skin[10].

Clinical manifestation

Intense itching is frequently the first symptom and precedes visible skin eruptions such as urticarial red raised, itchy bumps and vesicles or plaques. Predilection of skin manifestation appears in the periumbilical area, back and legs. PG usually affects women in the second or third trimester of pregnancy. Symptoms often disappearin several weeks or months after delivery. In reference to the hormonal status of a woman, the disease could flare exceptionally during menstruation and for those using hormonal oral contraception. The timing of the disease onset is significantly associated with gestational age at delivery and birthweight. An early onset of disease exposes the fetus to a longer period of sterile villitis and placental failure, resulting in a reduction in birthweight and an increased risk for low birthweight[11]. In addition, women manifesting with blisters during pregnancy are associated with preterm birth.

Diagnostic assessment

Pemphigoid diagnosis is determined by clinical symptoms and requires bioptic confirmation. The standard method is examination by an experienced dermatologist (anamnesis, subjective feelings of pain, pruritus). Another important examination during the diagnosis of this disease are blood tests (blood count, coagulation, biochemical tests) – electrophoresis of immunoglobulins, cytological examination from the base of the blister – "Tzanck test" (positive) histological and immunohistological examination of the skin biopsy sample. Additionally, an indirect immunofluorescence method of the patient's serum sample for the presence of antibodies against the intercellular substance (ICS), immunoblotting technique and determination of antibodies against desmoglein 3, and enzyme-linked immunosorbent assay (ELISA) may be necessary[12].

Treatment

Treatment can be complicated and prolonged depending on the timing of the diagnosis. No combination of therapeutic modalities provides an ideal outcome. The primary goal is to reduce itching and discomfort. If the symptoms are mild, they can be treated with anti-itch creams such as antihistamine products or topical corticosteroids and in the case of more severe symptoms, corticosteroids can be given perorally. Prednisone and Prednisolone treatments are preferred (optimal dose Prednisone 0.5 mg/kg/day), as these corticoids can be used in pregnant women due to the low number of adverse effects and poor transplacental passage. Non-drowsy products are also preferred including Cetirizine, Fexofenadine, and Loratadine. Corticoid systemic treatment should be prescribed with caution and at the lowest possible dose for the shortest exposure period[13]. The present prospective controlled study supports that glucocorticoids do not present major teratogenic risk in humans[14]. In utero exposure to glucocorticoids seems to contribute to a higher rate of preterm births and a lower birthweight, particularly when the exposure continues throughout the entire pregnancy[14]. No increase in the rate of major anomalies among live births plus elective terminations of pregnancy due to prenatally diagnosed anomalies between the glucocorticoids group compared to the control was found[14]. Cyclosporine downregulates T-cell function, and it has been used during pregnancy in organ transplant patients and in various autoimmune diseases with no association with increased risk of congenital malformations. Maternal and fetal follow-up is warranted due to risks of infection,

premature delivery, fetal growth restriction and maternal kidney changes becoming irreversible. Cyclosporine therapy during pregnancy should be carefully considered by the treating physician, but may be a safe alternative for patients with autoimmune disease refractory to conventional treatment. Continued monitoring of this patient population remains a key component to understanding the risk factors associated with cyclosporin exposure during pregnancy[15]. Cyclosporine treatment can be considered antenatally when treating severe and persistent PG unresponsive to topical and systemic glucocorticoids[16].

If the effect of therapy is insufficient or if there are repeated exacerbations, treatment with immunosuppressants orintravenous immunoglobulins (IVIG) and plasmapheresis is necessary. The use of IVIG is also a suitable option in pregnancy, but it is a very costly treatment. The use of Dapsone is not contraindicated but is one of the final options for PG therapy in pregnancy, especially in pregnant women who do not respond to corticosteroid therapy. The use of Tetracycline and Methotrexate is contraindicated in pregnancy.

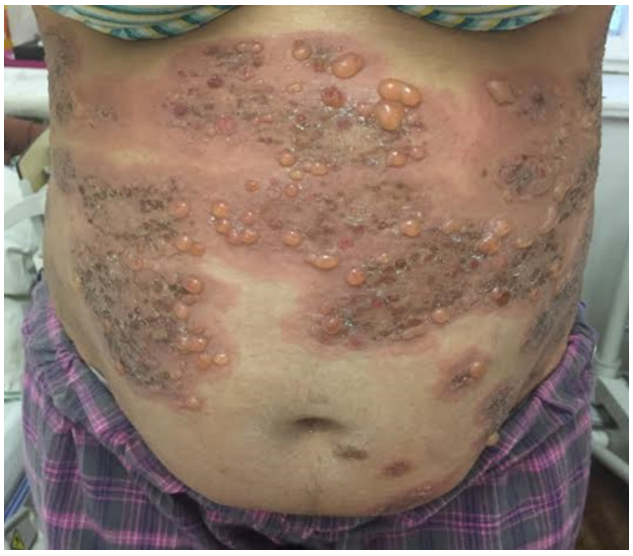

Fig. 1. Typical periumbilical bullous manifestation, pemphigoid blisters.

CASE-REPORT

A 27 year old female patient was diagnosed with PG in her first pregnancy in 2014 when blisters appeared at the 32nd gestational week. The diagnosis was proved histologically. She was subsequently treated with systemic corticosteroids. At the 36th week, a cesarean section was performed due to premature rupture of membranes and failure to progress the labor. In the following pregnancy in 2018, the first manifestations of the disease appeared in the 9th gestational week and the course of the disease was more severe. She complained of pruritus on the upper limbs, trunk and abdomen, followed in a few days by extensive seeding of erythematous plaques and blisters (Fig. 1 and 2). Local treatment with corticosteroids was not effective. Systemic corticosteroid treatment

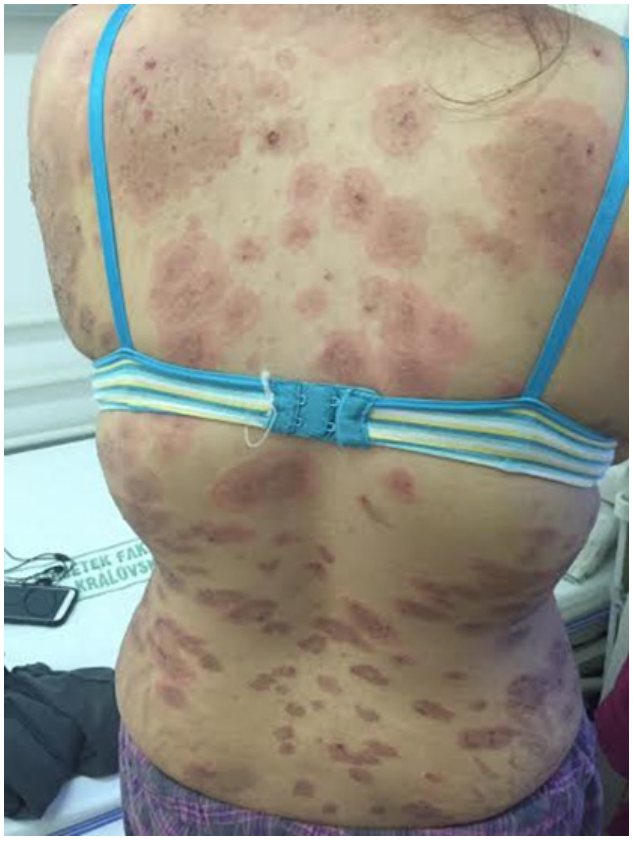

Fig. 2. Extensive urticarial lesions on the back.

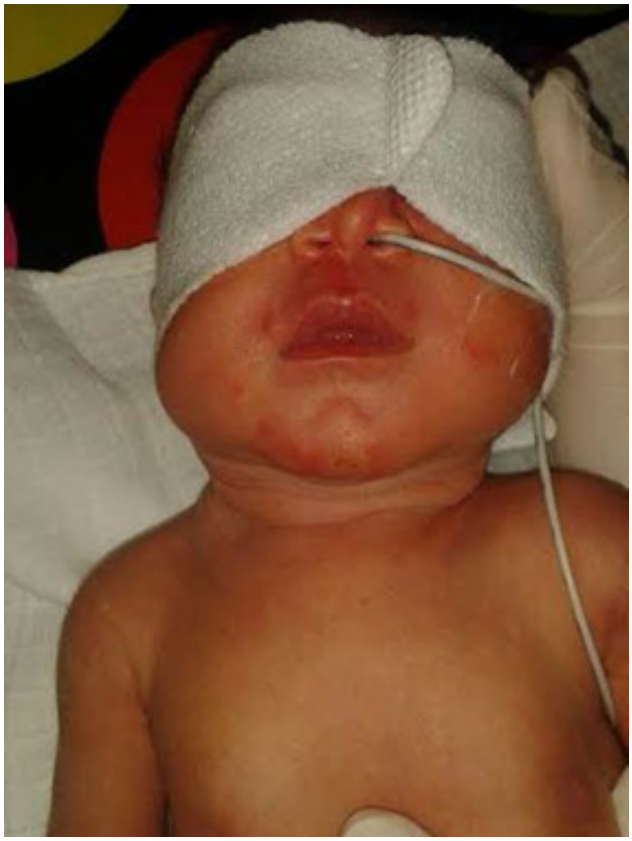

Fig. 3. Blisters on the face of the newborn.

(Prednisone 0.5 mg/kg) had to be initiated from the 14th gestational week, with gradual increase of doses, temporarily up to 0.7 mg/kg/day. New blistering appeared in the 16th gestational week, so we decided to add another immunosuppressive agent. Cyclosporine was chosen as an additive treatment, this medicament has no teratogenic effects on the dose of 1.5 mg/kg. After 4 weeks we were able to reduce Prednisone dose to 0.3 mg/kg. The patient developed diabetes mellitus with the need for treatment with oral antidiabetic drugs (Metformin 2x500 mg/day). Due to insufficient compensation insulin was added. In the 33rd gestational week, premature rupture of membranes occurred. No signs of inflammation were confirmed by the laboratory results. Antenatal corticosteroids for lung maturity were not administered due to acute termination of pregnancy by cesarean section (indication – premature rupture of membranes, risk of uterine rupture-pain in the scar). A healthy girl was born (2340 g/44 cm, Apgar 9-10-10). Small herpetiform vesicles subsequently developed on face of the baby on day 2 postpartum which spontaneously disappeared within 2 weeks after delivery (Fig. 3). On the 4th day after delivery, the patient-mother complained of pruritus on her palms and small urticarial eruptions on her hands and thorax. Lactation was stopped with Carbegolinum (4 doses of 0.5 mg of Cabergoline 12 h apart). The patient was discharged on day 5 postpartum to outpatient care and remained under the care of a dermatologist. After one month of delivery the patient still had new lesions and she was still treated with Prednisone and Cyclosporine. The newborn was regularly monitored, no complications in development occurred.

DISCUSSION

We describe a case of a pregnant patient with pemphigoid gestationis, including a rare complication in a newborn. Pemphigoid gestationis is an autoimmune dermatosis associated with pregnancy. PG usually affects women in the second or third trimester of pregnancy. Symptoms often disappearin several weeks or months after delivery. In reference to the hormonal status of a woman, the disease could flare exceptionally during menstruation and for those using hormonal oral contraception. An early onset of disease exposes the fetus to a longer period of sterile villitis and placental failure, resulting in a reduction in birthweight and an increased risk for low birthweight[11]. In addition, women manifesting with blisters during pregnancy are associated with preterm birth. Diagnosis made clinically in combination with biopsy of the lesions. Additionally, an indirect immunofluorescence method of the patient's serum sample for the presence of antibodies against the intercellular substance (ICS), immunoblotting technique and determination of antibodies against desmoglein 3, and enzyme-linked immunosorbent assay (ELISA) may be necessary[12]. Treatment can be complicated and prolonged depending on the timing of the diagnosis and the course of the disease. The primary goal is to reduce itching and discomfort. If the symptoms are mild, they can be treated with anti-itch creams such as antihistamine products or topical corticosteroids and in the case of more severe symptoms, systemic corticosteroids are needed. If there is a need to add another immunosuppressive therapy, Cyclosporine is an option as we did in our patient. Cyclosporine therapy during pregnancy should be carefully considered by the treating physician, but may be a safe alternative[15,16].

If the effect of therapy is insufficient or if there are repeated exacerbations, treatment with intravenous immunoglobulins (IVIG) and plasmapheresis may be needed. Benefit from systemic corticoid treatment in women with pemphigoid gestationis outweighs their potential perinatal harm such as preterm delivery and low birth weight. Oral antihistamines are usually used for itch management. No official guidelines were set except recommendations stated by French Society of Dermatology[17].

In the described case we had to gradually adjust the pharmacotherapy as recommended in the literature. Unfortunately, even the combined treatment did not completely resolve the situation, and a complication (as a side effect of the treatment) occurred – impaired sugar metabolism with the need for insulin treatment. In most recommendations, combination therapy is described as sufficient, but in our case, despite the treatment described above, there were manifestations even in the newborn, which is very rare. Fortunately, the manifestations were very discreet and the child's current condition is already quite normal.

Multidisciplinary coordination in treatment (obstetrician gynecologist, dermatologist, diabetologist and neonatologist) is required. Early diagnosis is essential to deploy optimal therapy with minimal impact on the course of pregnancy. Another important aspect of this disease is the impact on the patient's psychological state. It is important not to underestimate this component of treatment. The pregnant woman is under a great deal of stress in fear for the fetus, due to the often persistent pruritus, sleep disturbances and sometimes panic attacks have occurred. Although the aim is to minimize the administration of medication in pregnancy, consultation with a psychiatrist/psychologist is highly advisable for this case and also for the possibility of psychopharmacotherapy.

CONCLUSION

Pemphigoid gestationis is a severe disease requiring fast and accurate diagnosis and therapy. Due to the rarity of the disease both treatment and diagnosis can be challenging. Consulting a gynecologist-obstetrician is crucial and it is necessary that the patient is followed by both specialists. Concerns about systemic medication in pregnancy should not delay the initiation of therapy. Presence of PG in pregnancy is a risk factor for recurrence of PG in further pregnancy.

It is necessary to approach every dermatological problem in pregnancy very responsibly and in case of any ambiguity consult with a dermatologist to establish the final diagnosis and adequate therapy. It is often necessary for the patient to continue to be under the care of

a dermatologist, a diabetologist and often a psychiatrist after delivery.

ABBREVIATIONS

AEP, Atopic eruption of pregnancy; ELISA, Enzyme-linked immunosorbent assay; ICP, Intrahepatic cholestasis of pregnancy; IVIG, Polyvalent intravenous immunoglobulins; HLA, Human leukocyte antigen; MHC, Major histocompatibility complex; PEP, Polymorphic eruption of pregnancy; PG, Pemphigoid gestationis; SGA, Small for gestational age.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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