



Case Report

Pemphigoid Gestationis in a 15 Year Old Pregnant Patient, A Case Report and Literature Review

Emile Dabaj¹, Jana Abdo¹, Stephanie Yacoub^{1,*}, Rawad Halimeh¹, Zarouhie Bedoyan²
Joe Khalifeh¹

¹Department of Obstetrics and Gynecology, St George Hospital University Medical Center, University of Balamand, Beirut, Lebanon

²Department of Pathology, St George Hospital University Medical Center, University of Balamand, Beirut, Lebanon

Email address:

emile.dabaj@gmail.com (E. Dabaj), jana.abdo@gmail.com (J. Abdo), stephaniefyacoub@gmail.com (S. Yacoub),

rawad.halimeh@gmail.com (R. Halimeh), zzmeguerian@stgeorgehospital.org (Z. Bedoyan), joekhalifeh@gmail.com (J. Khalifeh)

*Corresponding author

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Abstract: Pemphigoid gestationis, previously known as herpes gestationis, is a rare autoimmune bullous disease that manifests in pregnancy. Upon presentation, patients complain of intense pruritis, urticarial plaques, vesicles and bullae that primarily affect the peri-umbilical area before spreading to involve the rest of the body. The accurate diagnosis of pemphigoid gestationis is made histopathologically on biopsies, based on the presence of sub-epidermal vesicles, as well as direct visualization of linear deposition of C3 at the basement membrane zone by using immunofluorescence staining on those biopsies. The mainstay treatment of the disease remains corticosteroids. Prompt recognition and provision of the appropriate management allow a reduction in both maternal morbidity as well as fetal adverse perinatal outcomes. Pathologic skin dermatoses and diseases of pregnancy are rare and have different presentations, treatment and prognoses. This literature review includes an up to date comparison on the presentation, diagnosis and treatment of dermatoses in pregnancy, in order to help with the discrimination. A case of pemphigoid gestationis in a 15 year old woman is described. This is the youngest reported age of presentation of pemphigoid gestationis, raising the question of whether maternal age is a factor that can affect the course and the severity of the disease.

Keywords: Pemphigoid Gestationis (PG), Herpes Gestationis, Pregnancy, Pruritis, Autoimmune, Major Histocompatibility Complex (MHC)

1. Introduction

Pemphigoid gestationis (PG), previously known as herpes gestationis, is a rare autoimmune bullous disease of pregnancy [1]. It occurs in approximately 1 in 50,000 pregnancies and mostly manifests during the second and third trimesters [2, 3]. In 20% of cases, patients can experience an initial onset of disease in the immediate postpartum period [4]. The typical presentation of PG is intense pruritis, urticarial plaques, vesicles and bullae that primarily affect the peri-umbilical area [1, 3, 5, 6]. These vesicles burst, resulting in painful erosions and hyperpigmentation. The distribution of disease then

spreads to include the chest, back and extremities and usually spares the mucous membranes and face [1, 3, 5, 6] PG is rarely associated with hydatidiform moles and chorion epitheliomas [1].

It results from an autoimmune process in which the major histocompatibility complex (MHC) Class II molecules are abnormally expressed on the placenta and cross-react with transmembrane proteins in the skin [7]. Diagnosis is made histo-pathologically based on the presence of sub-epidermal vesicles as well as visualization of linear deposition of C3 at the basement membrane zone by immunofluorescence of biopsies [8].

This article presents the case of a 15-year-old woman diagnosed with PG as well as a review of the literature including pathophysiology, diagnosis and treatment of this rare disease. To record, this is the youngest reported age at which a patient has been diagnosed with PG.

2. Case Report

A 15-year-old primigravid, Lebanese woman at 31 weeks and 5 days gestation as per last menstrual period, presented to the emergency room for evaluation of a diffuse pruritic rash that began to appear over the past 7 days. The eruption initially began as a single raised, red lesion in the peri-umbilical area that progressed to involve pruritic lesions on her arms, thighs, back and chest, sparing her palms and soles.

The patient reported normal fetal movements and denied experiencing any contractions.

Past medical and surgical histories were unremarkable. Patient denied cigarette smoking, alcohol intake, any exposure to illicit drugs and recent travel history. She did not have any known food or drug allergies. Her sole medications were perinatal vitamins. She was unaware of any family history of autoimmune disease or significant dermatologic conditions. She denied any recent illness, fever, chills, night sweats, nausea and vomiting.

Physical examination revealed generalized edematous eruptions with overlying vesicles and bullae, scattered over the abdomen, chest, flanks, arms and legs. No pustules were visualized. The oral mucosa, palms and soles were not involved. Figures 1, 2 and 3 depict the lesions noted on presentation.

Upon admission a non-stress test was reassuring with no uterine contractions. Obstetrical ultrasound showed a single live fetus in cephalic presentation, normal gross morphology, adequate amniotic fluid index, the placenta was located posteriorly with no evidence of previa and an estimated fetal weight of 1403g (3.09 lb). Doppler examination of the umbilical and middle cerebral arteries was normal. Trans-vaginal ultrasound showed a 35 mm long cervix with no evidence of funneling. Cervical exam revealed a cervix that was closed, posterior and long.



Figure 1. Lesions involving the peri-umbilical region.



Figure 2. Different stages of healing of several lesions. The black arrow shows a large vesicle (usually the earliest phase of a lesion in PG). The red arrow points to burst lesions with a hollowed center.



Figure 3. Classical hyperpigmentation seen in older lesions, depicted here on both upper thighs.

PCR for varicella zoster virus and rubella virus detected no DNA, and bacterial cultures showed no growth.

Histopathology reported the following: Two skin punch biopsy specimens were obtained from the left thigh, from lesional and peri-lesional skin, for hematoxylin and eosin stain and direct immunofluorescence study, respectively. Intraepithelial spongiotic vesicles containing many eosinophils and a few neutrophils were seen. There was superficial, dermal perivascular edema associated with perivascular lymphocytic inflammatory cell infiltrates. Numerous perivascular eosinophils extending to the interstitium and to the papillary dermis were identified. Figures 4-7 show the pathology staining of biopsies.

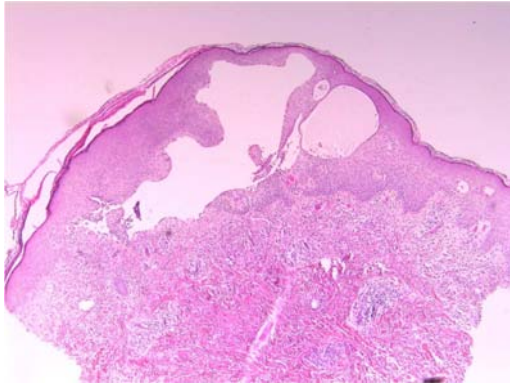


Figure 4. Low power view of sub-epidermal and intra-epidermal clefts with intra-epidermal vesicles.

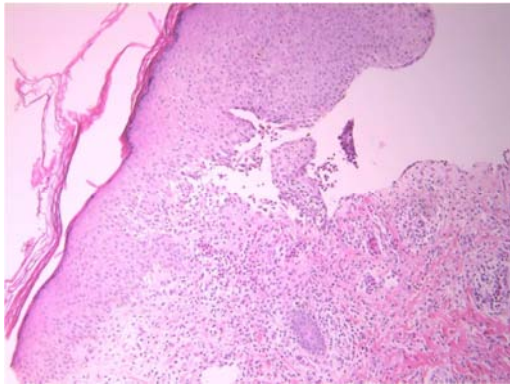


Figure 5. Inflammatory cells within the blisters.

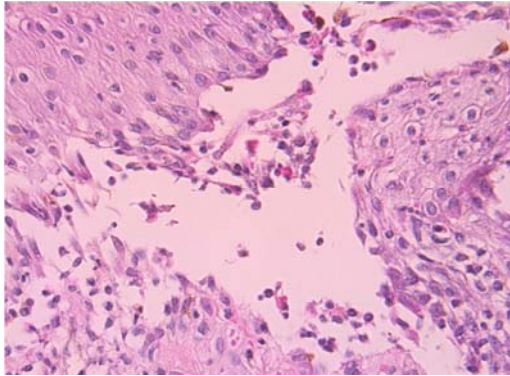


Figure 6. High power view of the characteristic eosinophilic red granules and inflammatory cells.

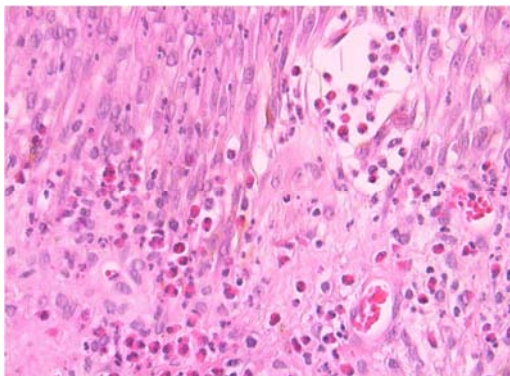


Figure 7. Dermis Eosinophils in the papillary dermis with intraepithelial eosinophils. Also noted, is eosinophilic spongiosis containing eosinophils inside.

Direct Immunofluorescence was performed using the anti-IgA, anti-IgG, anti-IgM, anti-C3 and anti-fibrin antisera, demonstrating a linear deposition of C3 along the dermo-epidermal junction. The other antisera were negative, hence the diagnosis of Pemphigoid Gestationis.

After the skin biopsies were taken, the patient was immediately initiated on 1mg/kg of prednisone daily until delivery.

Serial ultrasounds were performed and showed no abnormalities with a normal Doppler flow of both umbilical and middle cerebral arteries.

At 37 weeks of gestation, the patient presented in spontaneous labor and had an uneventful normal vaginal delivery of a living baby boy with a weight of 2010 g (4.43 lb). Upon careful examination, the baby had no evidence of any skin lesions.

The dosage of corticosteroids was gradually tapered in the postpartum period and was well tolerated. By one month postpartum, all skin lesions had completely resolved.

3. Discussion

In 75% of cases of Pemphigoid Gestationis, the disease is reactivated at the time of delivery. The relapsing and remitting nature of PG is believed to be due to progesterin's immunosuppressive properties and estrogen's ability to enhance antibody production. Towards the end of pregnancy, progesterin levels are elevated, depressing antibody production and may explain the reactivation of disease [5]. There is a 90% possibility that PG will recur again in subsequent pregnancies with symptoms that develop with a higher severity and earlier in the pregnancy [9]. There are also reports of skip pregnancies occurring in about 8% of patients [4, 5, 7]. Supporting the theory that sex hormones play a role in pathogenesis of disease, PG can also flare up during menstruation or with post-partum use of oral contraceptives [2, 5].

The pathogenesis of PG remains unclear. An association with the presence of MHC II Class HLA antigens had been identified with HLA-DR3 in 61-80% and HLA-DR4 in 52-53% of patients diagnosed with PG [10]. Women diagnosed with PG are also at an increased risk of developing other autoimmune diseases later in life. Graves' disease is the most common comorbidity with an incidence of 10% [11].

On the molecular levels, patients with PG have abnormally expressed MHC Class II expression in the placenta. These MHC II molecules contact the maternal immune system and result in an immune reaction against BP180 (also known as BPAG1 or collagen XVII, a structural protein in hemidesmosomes that link the epidermis and dermis) [6]. The attacking antibodies are directed against NC16A, the largest non-collagenous domain of BP180. A TH1 response promotes the formation of immunoglobulin G1 PG antibodies that fix complement and result in the classical complement cascade to result in linear C3 deposition at the dermo-epidermal junction. The tissue damage and vesicle formation follows due to chemo-attraction of eosinophils and their subsequent

degranulation [2, 6, 12, 13].

There are other, more common dermatologic causes than PG for pruritic cutaneous eruptions that occur during pregnancy. These include atopic eruption of pregnancy (AEP), polymorphic eruption of pregnancy (PEP) and intrahepatic cholestasis of pregnancy (ICP) [9, 12, 14, 15]. AEP is the

most common skin disease associated with pregnancy [15]. PEP was previously known as pruritic urticarial papules and plaques of pregnancy (PUPPP) [14]. Table 1 shows a summary between the major differences in these dermatoses of pregnancy.

Table 1. Description of the three more common dermatoses of pregnancy and their main difference from Pemphigod Gestationis. AEP: Atopic Eruption of Pregnancy.

	Time of presentation	Disease description	Difference from PG
AEP*	First and Second trimester [15]	Papular, eczematous [16] Lesions start on abdomen (similar clinical picture to PG)	Different time of presentation [15] Direct immunofluorescence studies of peri-lesional biopsies are negative in PEP [14]
PEP*	Last trimester (mainly primigravida patients) [14]	Poses no risks to the newborn No recurrences in future pregnancies [1, 16]	
ICP*	Last trimester [14]	Pruritis [14]	No visible lesions [16]

PEP: Polymorphic Eruption of Pregnancy. ICP: Intrahepatic Cholestasis of Pregnancy.

The gold standard for diagnosis of PG is direct immunofluorescence revealing linear deposition of C3 and IgG along the basement membrane zone [13]. The most common histo-pathological findings of PG include a subepidermal vesicle containing lymphocytes and eosinophils infiltrating the dermis in a perivascular distribution [18]. Early urticarial lesions may show edematous dermal papillae with a characteristic inverted teardrop shape [19]. Direct immunofluorescence of the peri-lesional skin shows linear C3 along the basement membrane zone at the interface of the epidermis and dermis. Immunoglobulin G, also termed herpes gestationis factor, is also present in 40% of cases [20]. ELISA technique is also used to detect circulating IgG against collagen XVII with 93% specificity and 100% specificity. It correlates with disease severity due to its quantitative nature [21]. Indirect immunofluorescence on the other hand, has 74% sensitivity and 80% specificity. 100% of PG patients can be diagnosed with the use of both indirect immunofluorescence and ELISA [22].

The patient in this case presented with the typical symptoms of PG. In order to differentiate PEP from PG, the described diagnostic measures were taken. Punch skin biopsies were obtained of both lesional and peri-lesional skin. The dermal papillae were edematous, subepidermal vesicles were found to contain lymphocytes as well as the finding of eosinophilic infiltrates of the dermis in a perivascular distribution. The histopathologic findings supported the diagnosis. Furthermore, direct immunofluorescence demonstrated a linear deposition of C3 along the dermo-epidermal junction. With diagnostic steps showing the classical findings of PG, the diagnosis was made.

The goals of treatment of PG are relief of symptoms as well as prevention of development of new blisters. Mild cases may be treated with topical glucocorticoid regimens but the treatment of choice for moderate to severe disease is oral glucocorticoids [23]. Most patients are started on an initial dose of 0.25-0.5mg/kg/day. If blisters continue to form within a few days of initiating treatment, the dose is increased until no new blisters appear. Doses of up to 180 mg of prednisone daily have been reported, but most patients respond to 20-40mg daily [2]. After 1-2 weeks, if symptoms are under

control, the cortisone dose is gradually tapered and if possible, discontinued altogether. After delivery, PG lesions usually disappear within 12-16 weeks with no scarring and so post-delivery oral cortisone treatment can be discontinued fairly soon. In the case of flare-ups, treatment is resumed [5].

The dosages of cortisone used in the treatment of PG do not cause a contraindication to breastfeeding [2, 6, 10]. Breastfeeding has been suggested to reduce the postpartum duration of PG due to the immunosuppressive effects of prolactin. Prolactin has been found to have a stimulatory effect on antibody production but overall, causes suppression of the immune system [9].

In the treatment of refractory cases, plasma exchange, immunoadsorption and intravenous immunoglobulin have been used in order to remove antibody from the serum, resulting in quick relief of symptoms [24].

Some other treatment options have been recommended for refractory cases of PG during the postpartum period but have a questionable safety profile. These agents include adjunctive cyclophosphamide, pyridoxine, gold and methotrexate [25].

Additional treatments include antihistamines, cool compresses and drainage of large blisters in order to prevent secondary infection. Different dressings using Vaseline gauze or silicone might also be beneficial for larger lesions [26].

The time of onset of the disease correlates with adverse pregnancy outcomes, unlike the extent of disease. An earlier onset of disease implies a longer period of placental failure that the fetus is exposed to, resulting in low birth weight and preterm labor [27]. Shornick and Black showed that 16% of pregnancies ended before 36 weeks and 32% ended before 38 weeks when associated with PG [11]. The small placental changes cause small for gestational age fetuses in women with PG, resulting in a high-risk pregnancy [9]. 10% of newborns develop mild urticaria and vesicular skin lesions due to the passive transfer of IgG from mother to fetus. The skin lesions resolve spontaneously [12]. It must be noted that when high doses of corticosteroids are given for an extended period of time, the newborn must be examined directly after delivery in order to exclude adrenal insufficiency [28].

In the vast research performed regarding the disease and the literature that describes this rare dermatosis, there have been no accounts of patients regarding young age. There have been no accounts of teenage patients and most cases describe patients in the typical reproductive age. This study raises the question of whether maternal age affects the severity or course of the disease.

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