An unusual and atypical presentation of early pemphigoid gestationis in primigravida: A unique case report

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Abstract
Pemphigoid gestationis (PG), also known as *herpes gestationis*, is a rare autoimmune blistering disease that presents in the second or third trimesters and during the immediate postpartum period. PG is presumably caused by circulating autoantibodies against bullous pemphigoid antigen 180 (BP180) within the basement membrane zone (BMZ). Clinical diagnosis is confirmed with a biopsy and positive direct immunofluorescence. PG tends to recur in subsequent pregnancies with an earlier and more severe presentation. Mild forms can be treated with topical antihistamines and corticosteroids and successful remission occurs with oral corticosteroids. Patients with PG are at greater risk of miscarriages, preterm delivery, still birth, small for gestational age (SGA), transient erythema and blistering. We report a rare case of early onset PG.

Keywords: Pemphigoid gestationis, Autoimmune, Sub epidermal blister, BP180.

Introduction
Pregnancy dermatoses are rare but unique dermatological conditions, which can occur at particular stage of pregnancy, and recur in subsequent pregnancies. Pregnancy dermatoses are clinical indicators of underlying autoimmunity or hormonal imbalance. They can be broadly divided into benign physiologic changes, or alterations in pre-existing skin diseases because of immune-hormonal changes, and pregnancy-specific dermatoses. Pregnancy-specific dermatoses represent a group of skin diseases that occur only during pregnancy and/or the immediate postpartum period. Severe pruritus represents the leading symptom commonly followed by a more widespread skin rash. Above all pregnancy-specific dermatoses are associated with high risk of foetal distress, foetal loss, miscarriages, small for gestational age (SGA), stillbirth and on. Pregnancy specific disorders pemphigoid gestationis (PG), polymorphic eruption of pregnancy (PEP), intrahepatic cholestasis of pregnancy (ICP), and atopic eruption of pregnancy (AEP).

Pemphigoid gestationis (PG), also known as *herpes gestationis*, is a rare autoimmune blistering disease with a reported incidence of 1:50,000 pregnancies.[1] It presents in the second or third trimesters and, in 15%–25% of cases during the immediate postpartum period. Milton coined the term herpes gestationis in 1872. PG is presumably caused by circulating autoantibodies against bullous pemphigoid antigen 180 (BP180) within the basement membrane zone (BMZ).[2] Pemphigoid Gestationis which is clinically similar to the pemphigoid group of autoimmune blistering and an immune response directed against different hemidesmosomal proteins affecting the adherence between the dermis and epidermis causing blistering of the skin and mucosal membranes. Clinically, PG is characterized by intense pruritus and polymorphic skin eruptions. Pruritus can emerge before skin lesions and remain the only symptom. In more severe cases, skin lesions develop including erythematous patches and plaques, sometimes followed by urticarial rash and blisters. Clinical diagnosis was confirmed with a biopsy and positive direct immunofluorescence. PG tends to recur in subsequent pregnancies with an earlier and more severe presentation. Mild forms of PG can be treated with topical antihistamines and corticosteroids and successful remission usually occurs with oral corticosteroids such as prednisone. Patients with PG are at greater risk of miscarriages, preterm delivery, still birth, small for gestational age (SGA) newborns and transient erythema and blistering.[3]

Case Report
A twenty-year-old primigravida with 4 months amenorrhea presented with multiple raised fluid filled lesions associated with intense itching was present over both upper extremities. Pruritic urticarial rash was the initial presentation of PG. multiple tense bullae over

forearm, antecubital fossa, periumbilical region and progressed to involve thigh of one-week duration. History of itching was present. No history of spontaneous rupture of blisters and no spontaneous healing. Itching was intractable intense and all lesions become flaccid, secondarily infected, painful, which further worsened the healing and new lesions developed to appear, but there was no mucosal complications till date noted.

Examination revealed multiple tense vesicles and bullae were present over flexural of both forearms, arms over an erythematous base. Urticarial plaques were also seen. Nikolsky sign and bulla spread sign were negative. Diffuse ill-defined hyperpigmented plaques with few papules seen over both the thighs. There were no Mucosal lesions of oral, conjunctiva, anogenital regions. Palms and soles were normal. Cardiovascular, respiratory, and renal functions were mormal. Systemic examination were within normal limits.

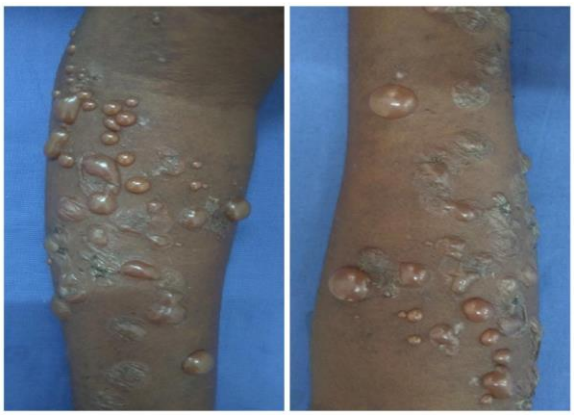

Fig. 1: Bulla over both forearms

Routine investigations including hemogram, liver and renal function tests, blood sugar levels and urine examination were within normal limits. Haemoglobin was 8 grams, and Tzanck smear did not showed any acantholytic cell but field was filled with eosinophils and neutrophils. The histopathological changes helps us to assess the disease severity as the pre bullous urticarial lesions may show edema of the upper and mid-dermis with a perivascular infiltrate of lymphocytes, histiocytes, and eosinophils and in bullous stage of PG subepidermal split formations and bullae become evident. Similar histological changes cannot differentiate PG from Polymorphic eruptions of pregnancy (PEP). also These findings were consistent with a diagnosis of PG but not specific as such changes can be seen in bullous pemphigoid hence, immunohistochemistry or other immunological investigations are required to confirm the diagnosis of PG. Direct immunofluorescence (DIF) or indirect immunofluorescence (IIF), enzyme-linked immuno- sorbent assay (ELISA), and C4d immunochemistry which is still experimental at stage. Basement zone antibodies IgG autoantibodies were seen in 30%–100% of cases. Diagnostic ELISA was highly specific (94% – 98%) and sensitivity of 86%–97% in the detection of BP180 antibodies in patients with PG.

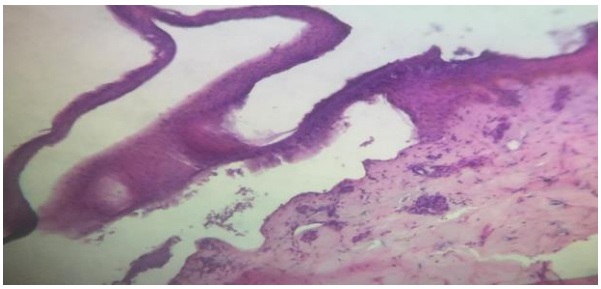

Fig. 2: Subepidermal bulla (10x HPE)

DIF showed a strong linear band of IgG and C3 along the basement membrane zone (BMZ). IgM, IgA and fibrinogen were negative. The DIF findings were highly suggestive of PG. The patient was started on oral prednisolone 30 mg daily along with supportive measures. Her condition improved and she did not develop any further lesions.

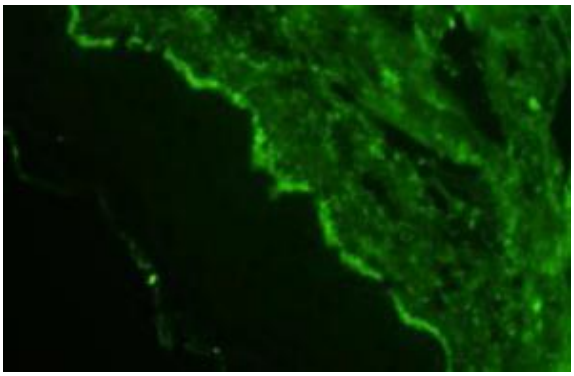

Fig. 3: Linear deposition of Ig G & C3

Discussion

Pregnancy dermatoses are challenging to treating dermatologists and gynaecologists as the disease onset and course, severity will be variable with period of pregnancy. Pregnancy specific dermatoses should be differentiated from other causes of pruritus like urticaria, drug hypersensitivity reactions, contact dermatitis and other eczemas, pityriasis rosea, pityriasis versicolor, and yeast

folliculitis, miliaria, and scabies. PG lesions mimics clinically and histologically bullous pemphigoid, which is characterized by deposition of autoreactive antibodies directed against two hemidesmo- somal proteins, BP180 and BP230, within the dermoepidermal junction, resulting in the formation of bullae and skin erosions.

Pregnancy specific conditions which closely mimic PG are Polymorphic eruption, atopic eruption, Intra hepatic cholestasis. PG mostly seen in multi parous women and mostly in second and third semester. PEP which commonly seen in first trimester sparing periumbilical region. Intra hepatic cholestasis in last trimester, associated with icterus and high foetal risks than PG, along with elevated bile acid levels and skin lesions are mainly secondary to scratching.

In the present case, the onset was seen in twenty years old primigravida, first trimester of Pregnancy, lesions were seen predominantly over upper limbs, fore arm, umbilicus and very few lesions over thighs. Responded well to topical and systemic corticosteroids and no recurrence during 6 months of follow up. The clinical diagnosis was confirmed with direct immunofluorescence.

Various pathogenetic mechanisms were proposed in favour of PG were which include abnormal expression of major histo- compatibility complex (MHC) class II placental trophoblasts and amnio chorionic stromal cells show an abnormal expression of major histo-compatibility complex (MHC) class II antigens allowing the presentation of BP180. HLA mismatch between mother and fetus triggers an immune response which initiates an allogenic response to placental BMZ, which then cross reacts with skin.

Which is also structural protein of hemidesmosomes linking the epidermis and dermis, found in placental tissue, in foetal membranes, and also in the basement membrane zone of the skin and placental tissue and foeal loss. The binding of these antibodies to the basement membrane of the skin triggers an autoimmune response that consists of complement activation, deposition of immune complexes, consecutive chemoattraction of eosinophil granulocytes, and subsequent degranulation, resulting in tissue damage and blister formation

Recent immunohistochemical studies have identified T helper (Th2) phenotype in the lesional skin of PG, that may be implicated in the recognition of self-antigens and production of pathogenic autoantibodies.[4] The close association with HLA-DR3 and HLA-DR4 represents an interesting statistical correlation, the significance of which is not yet clearly understood. The presence of anti-HLA antibodies in nearly all affected patients appears to be an epiphenomenon. Of great interest is the role of paternal antigens, which remains intriguing. This case being reported for its early onset at the end of 1st trimester and unusual site of onset of blisters sparing abdomen.

Pemphogoid gestationis lesions occurs with variable severity. Pruritus associated with eruptive polymorphic skin lesions, urticarial papules and annular plaques, followed by vesicles and finally large tense bullae on an erythematous background Skin lesions typically develop on the abdomen, characteristically involving the

Many patients experience remission during late pregnancy, sometimes followed by a flare immediately after delivery. The flare usually settles over a period of 4 weeks without Mild cases of PG can be treated with potent topical class III-IV corticosteroids.[5] Symptomatic cases can be given antihistamines and oral or systemic corticosteroids at a daily dose of 0.5 mg/kg, with an average 5 to 110 mg / day. Very severe cases high doses of corticosteroids and taper with IVIG, cyclosporin A, dapsone, azathioprine, or methotrexate (postpartum). Various foetal risks include small for gestational age (SGA) babies and preterm birth. Since most of the therapeutic agents were immunosuppressive drug toxicity will be common.

Vesicular, urticarial skin lesions in newborns caused by a passive transfer of IgG antibodies (neonatal pemphigoid).

Conclusion

PG is a rare, pruritic, vesicobullous dermatosis that can be easily confused with other dermatoses of pregnancy and biopsy for direct immunofluorescence is the preferred test for confirmation of diagnosis. Early recognition and treatment of PG with oral prednisone significantly reduces complications such as SGA and preterm delivery. Most of the cases PG were self-limiting, they become symptoms free after 6 months after treatment or disappear following pregnancy. Very severe cases which are steroid resistant may require IVIG, which has good safety profile for the mother and the fetus. Cyclosporine A on long term causes high blood pressure, renal insufficiency, bone marrow suppression the patients should be monitored. The disease severity and course out come vary with patients. Recurrenes are common in 33%-50% of pregnancies, around 8% of cases showed skipped pregnancies after PG in previous pregnancies. Persistent skin lesions of PG

following pregnancy were seen in few patients with duration ranging from 2wks to 12 yrs. In our case, PG seen in primigravida, and there was no family history of PG, onset was early, fore arm lesions were mostly tense blistering, secondarily infected, short course of steroid was given responded well.

Consent

Written informed consent has been obtained from all patients for the publication of their images.

Disclosure

The authors report no conflicts of interest in this work.

Acknowledgement

Nil.

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