Herpes gestationis associated with normal pregnancy or complete hydatiform mole: report of three cases

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Summary

Herpes gestationis, also known as pemphigoid gestationis, is a rare autoimmune blistering disease associated with pregnancy and puerperium. Most cases are related to physiological pregnancies, otherwise, single cases have been described in association with molar pregnancies and trophoblastic tumours. We herein describe three cases of HP, two associated with a physiological gestation and one with a complete hydatiform mole.

KEY WORDS: herpes gestationis; pemphigoid gestationis; autoimmune blistering disease.

Introduction

Herpes gestationis (HG), also known as pemphigoid gestationis, is a rare autoimmune blistering disease associated with pregnancy and puerperium. Single cases have been described in association with molar pregnancies and trophoblastic tumours (1). We herein describe three cases of HP, two associated with a physiological gestation and one with a complete hydatiform mole.

Case 1

A 33-year old Moroccan woman presented at our Dermatologic Clinic for evaluation of pruritic itching plaques of the thighs developed at the 35th week of her second gestation and spreading to the abdomen and arms. The patient referred of good health during the previous pregnancy and denied fever or other systemic symptoms. Physical examination revealed erythematous-to-hyperpigmented plaques of the thighs and abdomen surrounding the umbilical area (Figure 1A). No mucosal lesions were observed.
A punch biopsy was performed on the left thigh. Hematoxylin and eosin stain revealed irregular epidermis with foci of parakeratosis. Vacuolopathy and necrosis of the basal layer were present without evidence of obvious subepidermal vesiculobullae. Extravascular erythrocytes involved the dermal papillae while mixed inflammatory infiltrate, composed by lymphocytes and eosinophils, occurred at both superficial and intermediate dermis (Figure 1B). Direct immunofluorescence demonstrated a linear deposition of C3 at the basement-membrane zone. Additionally, positivity for anti-BP180 antibodies (30.9 U/mL, normal range < 9 U/mL) was detected by enzyme-linked immunosorbent essay (ELISA) on plasma. Therefore, histological and immunological findings confirmed the clinical suspect of HG. Given the number and extent of skin lesions Fusidic Acid 2% and Triamcinolone 0.03% cream twice daily were prescribed for 14 days leading to complete resolution of the dermatosis by the 37th week of gestation.

Case 2

A 27-year old Moroccan woman was referred to the emergency care unit of the Department of Gynecology and Obstetrics because of vaginal bleeding after an uncertain period of amenorrhea associated to morning sickness. She referred a positive result of the pregnancy test performed at home two days before.
It was found an enlarged uterus with bleeding from the portio at gynecological exam; no pain or other symptoms were signaled.
The patient underwent blood tests that showed a Beta Human Chorionic Gonadotropin (β-HCG) of 132.459 UI/l (normal range after 3 weeks of pregnancy: 9-130 mUI/ml). The transvaginal ultrasonography pointed out a “honeycombed uterus” in absence of gestational sac or embryogenic findings; on right ovary a cystic-like lesion of 7 centimeters was found. These features

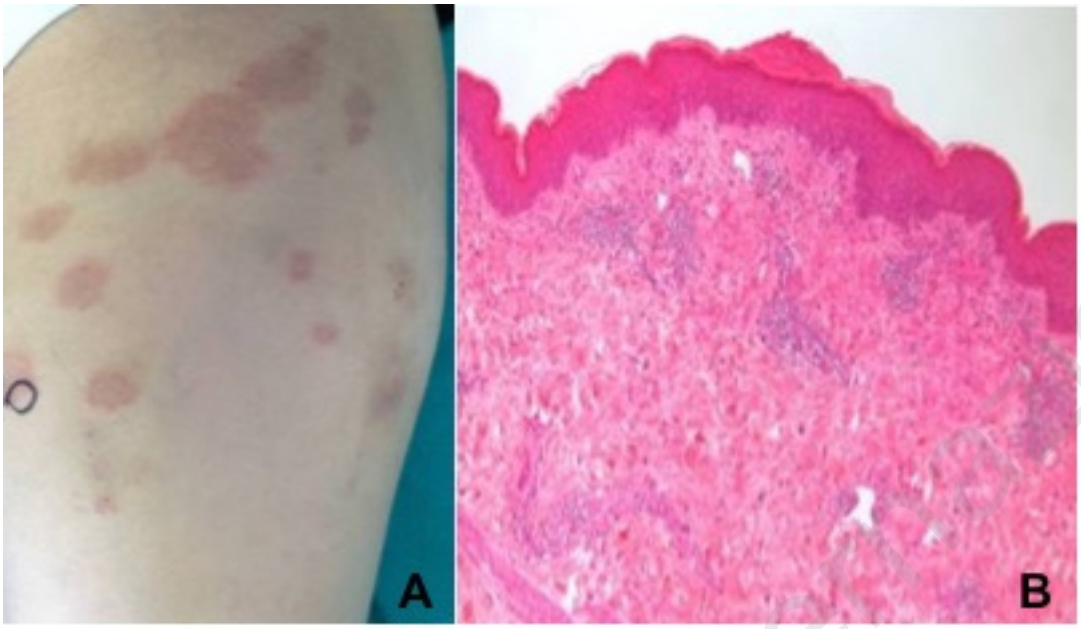

Figure 1, Case 1 - A) Erythematous-to-hyperpigmented plaques of the thighs. B) Irregular epidermis with foci of parakeratosis. Vacuolopathy and necrosis of the basal layer without evidence of obvious subepidermal vesiculobullae. Extravascular erythrocytes in the dermal papillae and mixed inflammatory infiltrate composed by lymphocytes and eosinophils at both superficial and intermediate dermis (4X magnification).

strongly suggested the diagnosis of a complete hydatiform mole.

After two days of hospitalization the patient was referred to a dermatologist consult for the appearance of itching brownish plaques of the thighs, legs and feet (Figure 2A). Few days after the first consult different bullous elements appeared on thighs and legs.

The punch biopsy performed on the left leg showed a large subepidermal bulla occupied by inflammatory infiltrate rich in eosinophilic granulocytes, accompanied by fibrin and erythrocytes. Eosinophils were present also in the dermis, both perivascular and interstitial (Figure 2B). In this case, direct immunofluorescence identified linear deposition of both C3 and IgG

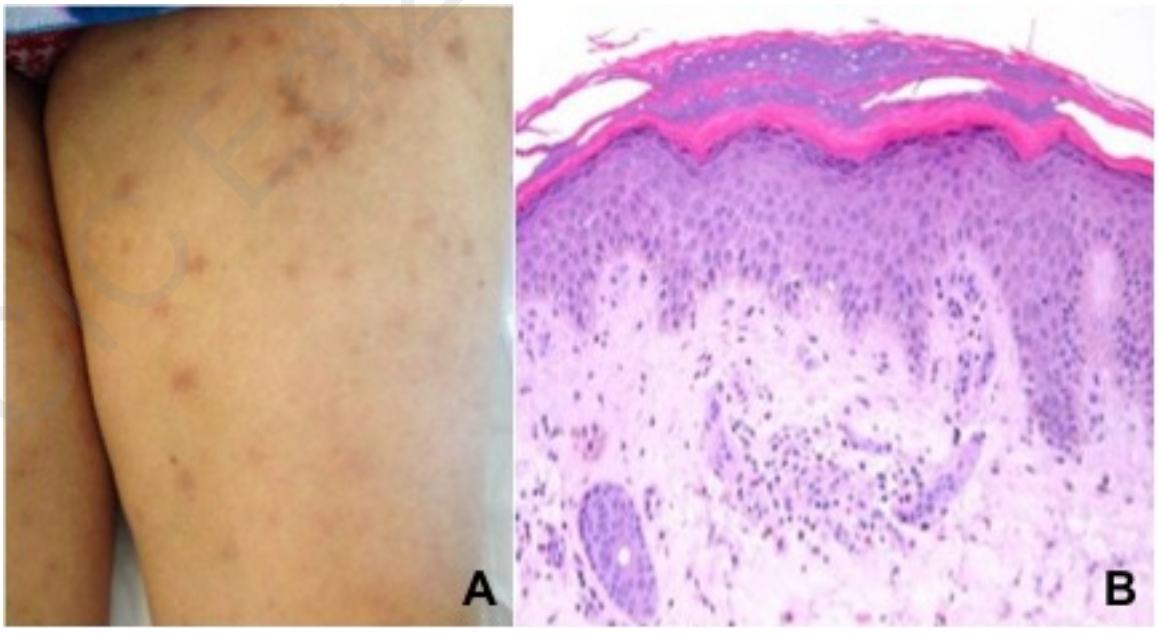

Figure 2, Case 2 - A) Itching brownish plaques of the thighs. B) Large subepidermal bulla occupied by abundant inflammatory infiltrate rich in eosinophilic granulocytes, accompanied by fibrin and erythrocytes (10X magnification).

at the basement-membrane; ELISA indices were again positive for anti-BP180 antibodies (56 U/mL, normal range < 9 U/mL).
The diagnosis of HG with complete hydatiform mole was made. The patient underwent uterine hysterosuction and curettage; following treatment with methotrexate was performed (50 mg by intramuscular injection repeated every 48 hours for a total of four doses). The value of β-HCG was 10.256 U/L 48 hours later. The patient was discharged with estroprogestinic therapy; β-HCG test was monitored until persistent negativity.
After two weeks of treatment the dermatosis was completely remitted.

Case 3

A 33-year old Moroccan woman presented at our Dermatologic Clinic with history of pruritic plaques of the abdomen developed at 36th week of her third gestation. The patient referred previously good health during pregnancy and denied fever or other systemic symptoms. After delivery the lesions spread to legs and arms.
At the time of presentation, physical examination revealed confluent erythematous and targetoid plaques of abdomen, back, arms and legs (Figure 3A). Multiple tense vesicles and bullae were found on feet, ankles, hands and wrists. No mucosal lesions were observed.
The newborn was in good health with no lesion observed.
A punch biopsy was performed on the right thigh. Despite clinical presentation, the skin biopsy showed normotrophic and normokeratotic epidermis without subepidermal vesiculobullae. Only the superficial dermis displayed a subtle perivascular inflammatory infiltrate including lymphocytes and occasional eosinophilic granulocytes. Nonetheless, direct immunofluorescence demonstrated a linear deposition of C3 at the basement-membrane zone (Figure 3B) diagnostic for autoimmune disease.
Additionally, positivity for anti-BP180 antibodies (79.3 U/mL, normal range < 9 U/mL) was detected by ELISA on plasma. Therefore, histological and immunological findings confirmed the clinical suspect of HG.
Given the number and extent of skin lesions, the patient underwent high dose systemic steroid therapy (intravenous methylprednisolone 1 mg/kg/die). No new vesicles or bullae were found after two days of therapy; progressively, the dose of systemic steroid therapy was reduced, and the patent was discharged after 10 days of hospitalization.
Oral methylprednisolone (dose of 0.5 mg/kg/die, progressively reduced) was prescribed leading to complete resolution of the dermatosis 15 days later.

Discussion

Herpes Gestationis (HG) is a rare autoimmune blistering disease associated with pregnancy and puerperium. The disease occurs in 1:50.000 pregnancies with no difference in racial distribution (1).
Usually symptoms start during the second and third trimester, although skin eruption may appear clinically during postpartum or in case of molar pregnancies and trophoblastic tumours (2). Five previous cases in which HG was associated with hydatiform mole have

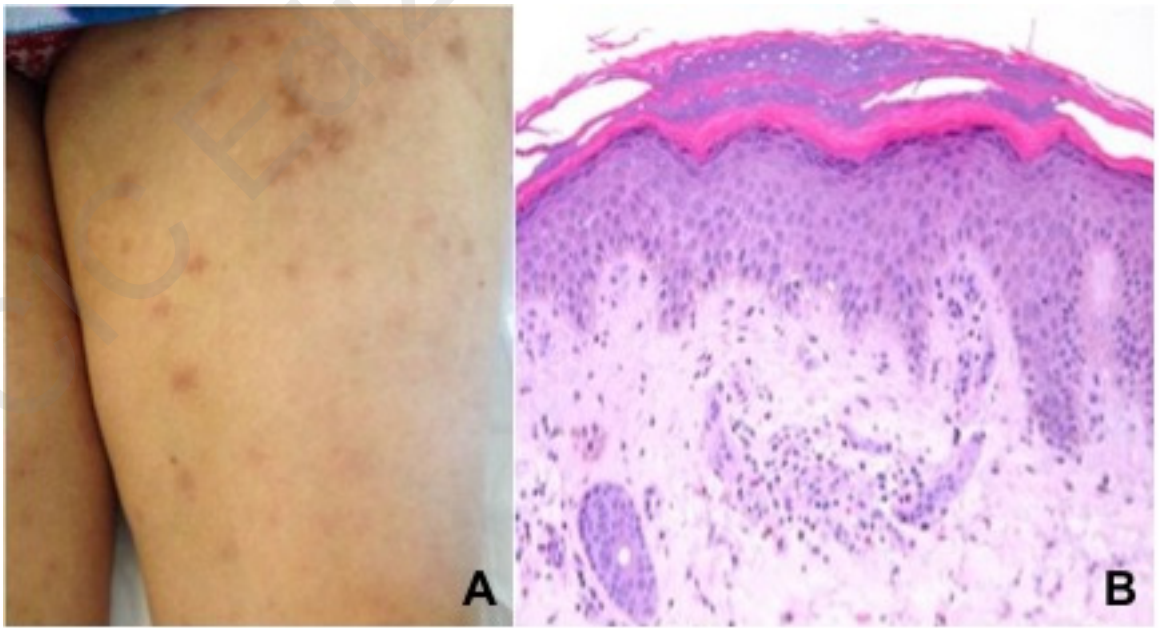

Figure 3, Case 3 - A) Multiple tense bullae of the arms and legs and Itching brownish plaques of the abdomen. B) Linear deposition of C3 at the basement-membrane zone (10X magnification) at immunofluorescence.

been reported so far (2, 3-6). A case of HG revealing a denial pregnancy (7) and a case post-abortion (8) have also been described.

Intense abdominal itching usually begins in the umbilical area in association to erythematosus papules and plaques, spreading to the abdomen or thighs and rarely to the whole body. These lesions can be followed by small vesicles or large blisters with a thick roof after few weeks however some patients do not present blisters at all, as described in our first case.

Facial and mucosal lesions are rare but usually associated with more persistent disease (1).

Although many patients improve just prior delivery, about 75% of patients flare at the time of delivery. Recurrence of HG during subsequent pregnancies is common and flares with menses or oral contraceptive agents may also occur (9).

The pathogenesis, similarly to bullous pemphigoid, involves autoantibodies that are directed against the non-collagenous domain (NC16A) of bullous pemphigoid antigen 2 (BPAG2 also known as BP180 or Collagen XVII). It is hypothesized that in patients with HG major histocompatibility (MHC) II antigens normally not found in the placenta (10) may initiate an immune response that cross-reacts with maternal skin. Antibodies against BP230 protein have been detected in about 10% of patients although HG is considered as a bullous pemphigoid developed in pregnant female (1, 9). A more rapid and less severe disease course may cause the failure in anti BP230 antibody production as these autoantibodies are considered a secondary phenomenon after disturbance of the cell membrane integrity by anti-BP180 antibodies (11). Measurement of serum BP180 antibodies level is useful in quantify disease activity and response to treatment.

Diagnosis of HG often needs hystopathological confirmation on skin biopsy. A subepidermal vesicle surrounded by an inflammatory infiltrate of histiocytes and eosinophils is the usual finding while direct immunofluorescence shows linear C3 deposition along the basement membrane zone. Linear IgG positivity is detected in about 25-50% of the samples.

The most important differential diagnosis for HG is represented by the other itchy dermatoses of pregnancy which include atopic eruption of pregnancy, polymorphic eruption of pregnancy and intrahepatic cholestasis of pregnancy (ICP). The first is an atopic condition, most likely to occur on a background history of personal or familial atopy, and it presents in the first delivery; polymorphic eruption of pregnancy, also known as pruritic urticarial papules and plaques of pregnancy, is a pruritic condition that occurs late in the third trimester, involving the abdomen but sparing the umbilical region. The latter is associated with multiple gestations and negative immunofluorescence essay on lesional skin biopsy. ICP presents in the last trimester with itching and abnormal liver-function tests leading to secondary scratching lesions or even prurigo nodularis (12).

The risk of prematurity and fetal growth restriction is greater in HG compared to normal population and this seems to be associated with mild placental failure caused by BP180 antibodies. No congenital abnormalities have been linked to the disease (1). Very rarely self-limited vesicular lesions may appear in newborns of affected mother within few days from delivery (13).

Initial treatment during pregnancy is with oral antihistamines, topical or systemic steroids. After delivery ciclosporin, azathioprine, dapsone, methotrexate and plasmapheresis can be considered for severe disease (12). Preventive off-label treatment with rituximab has also been suggested (14). In case of HG associated with trophoblastic tumors hysterosuction and curettage followed by treatment with methotrexate is needed.

HP is a rare gestational disease and the association with molar diseases is even rarer. Clinical presentation is proteomic and clear blisters can be absent; also, histology and immunofluorescence cannot be diriment.

Conclusions

HP is a rare gestational disease; we hope that these cases will help gynecologists and dermatologists to diagnose and cure promptly other patients with similar presentations.

Declarations of interest

None.

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