CASE REPORT

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Pemphigoid gestationis. Case report Penfigoide gestacional. Reporte de caso

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ABSTRACT

Pemphigoid gestationis, formerly known as herpes gestationis, is a rare, blistering, autoimmune, pregnancy-specific dermatosis. Although the etiology is not fully understood, most patients develop antibodies against 180 kDa transmembrane hemidesmosomal protein. The defining symptoms of the disease are intense itching and urticarial lesions that evolve into painful blisters. Lesions begin in the periumbilical region in 90% of cases and spread rapidly to other areas of the body, except for the head and mucous membranes. It is most frequent in the second or third trimester. In skin biopsy specimens, direct immunofluorescence staining validates the diagnosis. Topical corticosteroids can be used to treat severe cases. A case of pemphigoid gestationis is presented.

Key words: Pemphigoid gestationis, Dermatosis, Pregnancy, Pemphigus

RESUMEN

El penfigoide gestacional, antes conocido como herpes gestacional, es una dermatosis rara, ampollosa, autoinmune y específica del embarazo. Aunque la etiología no se conoce del todo, la mayoría de los pacientes desarrollan anticuerpos contra una proteína hemidesmosomal transmembrana de 180 kDa. Los síntomas que definen la enfermedad son el picor intenso y las lesiones urticariales que evolucionan hacia ampollas dolorosas. Las lesiones comienzan en la región periumbilical en el 90% de los casos y se extienden rápidamente a otras zonas del cuerpo, a excepción de la cabeza y las mucosas. Es más frecuente en el segundo o tercer trimestre. En las muestras de biopsia de piel, la tinción de inmunofluorescencia directa valida el diagnóstico. Los corticoides tópicos pueden ser utilizados para tratar los síntomas leves, mientras que los corticoides orales y los antihistamínicos deben usarse para tratar los casos graves. Se presenta un caso de penfigoide gestacional. Palabras clave. Penfigoide gestacional, Dermatosis, Embarazo, Pénfigo

INTRODUCTION

Pemphigoid gestationis, previously known as herpes gestationis, is a rare cutaneous, bullous, autoimmune disorder of pregnancy first described in 1872⁽¹⁾. Most cases occur in the second or third trimester, with reports of a few isolated cases during the first trimester and puerperium. The main clinical manifestations are tension skin blisters with erythematous plaques, similar to those described in urticaria, accompanied by pruritus^(2,3). The clinical manifestations and laboratory findings are similar to bullous pemphigoid and its exact pathogenesis is still unknown⁽¹⁾. A case of pemphigoid gestationis is presented.

CASE REPORT

A 31-year-old female patient, gestation II, para I, with an active pregnancy of 25 weeks, consulted for presenting intense pruritus of approximately 12 days of evolution, associated with urticaria and edematous rash, initially in the peri-umbilical area, which then spread to the rest of the abdomen, thorax, and upper and lower limbs. The pregnancy had been conceived naturally and had not presented any complications up to that moment. She denied a personal history of skin disorders, autoimmune diseases, drug/food allergies or fever. She also denied any significant family history.

On physical examination, the patient exhibited extensive erythematous-edematous plaques, similar to urticaria, polymorphic, pink, with central erosions, crowned by tense vesicles, filled with clear fluid and



FIGURE 1. CUTANEOUS LESIONS, ERYTHEMATOUS PLAQUES, VESICLES, AND EROSIONS IN DIFFERENT ANATOMICAL LOCATIONS, AT 25 WEEKS OF PREGNANCY.

scattered hemorrhagic crusts on abdomen, thorax and upper and lower extremities. The vesicles were predominantly located around the umbilical scar and both lower limbs. No mucosal lesions were observed. Nikolsky's and extension signs of the vesicles were negative.

Hematology, liver and renal function, electrolytes, C-reactive protein, antistreptolysin, glycemia, urine examination, and thyroid tests were within normal limits. Obstetric ultrasound was reported normal with a male fetus in accordance with gestational age and normal amniotic fluid volume.

Skin biopsy was performed from the edge of the lesion on the right lower extremity. Histology showed that the dermoepidermal blister contained eosinophils with some lymphocytes and neutrophils within them. In addition, subepidermal spongiosis and perivascular lymphocytic infiltrate with granulocytes without acantholysis. Direct immunofluorescence showed positive linear staining for C3 along the basement membrane, with absence of IgA, IgG, and IgM. These results confirmed the diagnosis of pemphigoid gestationis.

In view of the findings, treatment was started with oral prednisolone (0.5 mg/kg/day), topical steroids and oral antihistamines. The clinical response was satisfactory, with a decrease in pruritus and gradual improvement of the skin lesions, which finally subsided without recurrence. The patient was discharged after 7 days with progressively decreasing doses of prednisolone and maternal-fetal surveillance.

The evolution of the pregnancy was uncomplicated, and the delivery was spontaneous resulting in a live male newborn of 3,200 grams with Apgar scores of 7 and 9 points at one minute and 5 minutes, respectively. The neonate had no skin lesions. The patient was discharged in satisfactory condition after 24 hours with no evidence of recurrence of the condition. Treatment was discontinued 15 days after the puerperium and she remained asymptomatic 6 months after discontinuation of treatment.

FIGURE 2. MICROSCOPIC IMAGE OF PEMPHIGOID GESTATIONIS. A) SUBEPIDERMAL UNFOLDING WITH FIBROUS MATERIAL, EOSINOPHILS, LYMPHOCYTES, AND NEU-TROPHILS WITHIN AND IN THE SUPERFICIAL DERMIS. HEMATOXYLIN-EOSIN STAIN, 10X). B) DERMIS WITH POLYMORPHONUCLEAR NEUTROPHILS AND PERIVASCULAR INFLAMMATORY INFILTRATE OF THE DERMIS (HEMATOXYLIN-EOSIN STAIN, 100X).



Figure 3. Direct immunofluorescence image showing linear positivity of C3 deposits along the dermoepidermal junction, with absence of IGG.



DISCUSSION

Pemphigoid gestationis is a rare cutaneous blistering disease with an incidence of approximately 1 case per 50,000 pregnancies⁽⁴⁻⁷⁾. The pathogenesis is autoimmune, and the triggering cause is unknown, with involvement of the dermoepidermal junction leading to blistering. The pathogenesis is similar to bullous pemphigoid. Its occurrence is associated with autoreactive IgG antibodies against BP180 protein (also known as BPAG1 or collagen XVII) and, partially, against BP230 protein, which are hemidesmosomal proteins at the dermoepidermal junction⁽⁸⁻¹⁰⁾. This leads to disconnection between dermis and epidermis, inflammation, and vesicle formation.

BP180 protein is expressed in skin, trophoblast, and amniotic stromal cells⁽⁹⁾. Its abnormal expression of major histocompatibility complex class II antigens on placental stromal cells leads to the presentation of BP180 protein to the maternal immune system, which recognizes it as foreign. This leads to the production of IgG antibodies that cross-react with BP180 proteins, causing inflammation and blistering. Pemphigoid gestationis is associated with HLA-DR3 and HLA-DR4 haplotypes of maternal class II antigens⁽¹⁾.



The most common manifestations of pemphigoid gestationis are pruritus and erythematous urticarial plaques. The latter initially appear as annular plaques and pruritic papules followed by large, tense vesicles with an erythematous base. They usually appear initially in the periumbilical area and later spread to the rest of the trunk, thorax, upper and lower extremities and even hands and feet. However, there are no dermatological alterations on the face and mucous membranes⁽¹¹⁾. In some patients, severe pruritus may be the only symptom, which makes diagnosis even more difficult⁽³⁾.

The cutaneous histologic changes of pemphigoid gestationis depend on the phase of the disease. The early phase is characterized by edema of the superficial and deep dermis with perivascular infiltrate of lymphocytes, histiocytes and eosinophils. In the bullous phase, there are subepidermal blisters filled with eosinophils and mixed perivascular infiltrate⁽¹⁾. These findings are nonspecific and can be observed in other dermatoses. The specific diagnostic test is direct immunofluorescence of the perilesional area, characterized by linear deposits of complement C3 and less frequently IgG, along the basement membrane. C3 deposits are present in all cases, while IgG deposits appear in 25 to 50% of cases^(1,4). Indirect immunofluorescence and ELI-SA tests for circulating IgG antibodies against BP180 protein may also be useful for diagnosis and monitoring of disease activity⁽²⁾.

In the early phase, pemphigoid gestationis is difficult to distinguish from other dermatoses of pregnancy, including polymorphous rash, atopic rash, and intrahepatic cholestasis⁽⁵⁾. Polymorphous eruption of pregnancy shares clinical features such as onset, location, pruritus, and urticarial morphology, but usually appears late in pregnancy. Atopic rash is the most common dermatosis in pregnancy and appears in the first and second trimester. Eczematous or papular skin lesions occur mainly on the trunk and extremities. Direct immunofluorescence findings are what allow the differential diagnosis to be made between the three conditions. Intrahepatic cholestasis of pregnancy is characterized by intense pruritus. Skin lesions secondary to scratching are excoriations or pruritic nodules, usually located on the extremities. The diagnosis is confirmed by elevated bile acid levels and abnormal liver function tests^(12,13).

Bullous pemphigoid and pemphigoid gestationis share similar clinical, histopathological, and immunological features⁽¹²⁾. Pemphigoid gestationis shows association with HLA-DR3 and HLA-DR4, whereas bullous pemphigoid is associated with HLA-DQ3. However, the latter appears at older ages, whereas pemphigoid gestationis is exclusively related to pregnancy⁽³⁾.

Pemphigoid gestationis can persist or worsen due to sudden variations in antibody concentrations and hormonal fluctuations. Therefore, it may recur in subsequent pregnancies, during menstruation or when progesterone-containing oral contraceptives are used⁽⁵⁾. There are also reports of cases associated with choriocarcinoma and hydatidiform mole⁽¹⁴⁻¹⁷⁾. Recurrences in subsequent pregnancies have been described in 33% to 50% of patients, with generally earlier onset and more severe symptomatology^(1,2). The most common obstetric complications are intrauterine growth restriction of the fetus and preterm delivery^(4,16,18).

The main goal of treatment is to reduce pruritus and prevent the formation of new blisters. In mild cases, topical corticosteroids and oral antihistamines can be used. In severe cases, oral corticosteroids such as prednisone and prednisolone are preferred as they are inactivated by the placental enzyme 11-β-hydroxysteroid dehydrogenase, producing lower fetal concentrations. Both betamethasone and dexamethasone are not metabolized and are less suitable for treatment⁽⁹⁾. Oral treatment with prednisolone starts at a dose of 0.5 mg/kg/day, which is gradually reduced according to clinical improvement⁽¹⁾. The duration of treatment should be individualized and depends on remission. The use of second-generation histamines is also recommended to control pruritus. In cases appearing in the puerperium there are more therapeutic options, such as intravenous immunoglobulin, azathioprine, dapsone, cyclosporine, pyridoxine, minocycline, nicotinamide, immunoadsorption, rituximab, erythromycin, cyclophosphamide, methotrexate, and plasmapheresis^(9,19).

It is necessary to remember that both pemphigoid gestationis and the treatment administered to pregnant women can affect fetal well-being. Most cases with pemphigoid gestationis have healthy newborns at term, delivered vaginally or abdominally for obstetric indications. Due to



passive maternal-fetal transfer of antibodies, 10% of neonates may develop skin lesions. In the first trimester, prednisolone may increase the risk of malformations, especially orofacial clefts, and in the last trimester, it may cause intrauterine growth retardation, eclampsia, and preterm delivery. However, there is no increased risk of stillbirths and spontaneous abortions^(13,20).

In conclusion, pemphigoid gestationis is a rare autoimmune skin condition that is most common in the second and third trimester of pregnancy. It is necessary to be aware of this condition when a pregnant woman presents with pruritus and urticaria-like or vesicular skin lesions, so that treatment can be initiated in a timely manner. Treatment consists of topical or systemic corticosteroids plus antihistamines depending on the severity of the clinical picture.

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