HERPES GESTATIONIS

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Herpes gestationis (HG), also known as pemphigoid gestationis or gestational pemphigoid, was first identified in 1872 by John Laws Milton, and is the most clearly characterized dermatosis of pregnancy. HG is a rare autoimmune bullous disease of pregnancy and the puerperium. It has been rarely associated with choriocarcinoma and molar pregnancy. The term *herpes* is used because of the frequent presence of grouped or herpetiform lesions. HG has an estimated incidence of 1 in 50,000 pregnancies worldwide [1]. HG shows a strong genetic linkage to HLA-DR3 and DR4 [2,3]. Some studies have shown that 61–80% of HG patients express DR3, 52–53% express DR4, and 43–50% express both MHC II genes. It usually affects multiparous women in late pregnancy, but it may begin early in pregnancy or within a few weeks postpartum. Common sites of involvement are the abdomen and the extremities. It is caused by the development of IgG1 antibodies to the basement membrane protein BP-180 [4–6].

A 26-year-old primigravida was admitted from the emergency department with 38 weeks' amenorrhea, and a 1-month history of pruritic vesiculobullous lesions all over her body, including her back and feet, and bilateral foot edema. She also complained of decreased fetal movements over the previous 3 days and fever since the previous day. The patient had been taking oral steroids (prednisolone; Wysolone; Wyeth Ltd., Mumbai, India; 40 mg once a day) for the past month and chlorpheniramine maleate tablets for 10 days, as well as using Condy's compresses and framycetin sulfate 1% cream (Soframycin; Aventis Pharma Ltd., Mumbai, India) locally on the vesicular lesions for the past month, as prescribed by her physician. However, the patient had experienced only minimal relief.

The patient was febrile, with a pulse rate of 110 beats/min and a blood pressure of 130/80 mmHg. There were vesiculobullous lesions all over her body, including her abdomen, back, limbs and breast. She also had bilateral foot edema (Figure). Her oral mucosa was normal. Abdominal examination revealed a uterine height corresponding to 34 weeks' gestation with cephalic presentation, decreased liquor, and a regular fetal heart rate of 142 beats/min. Speculum examination revealed a healthy cervix and vagina. No lesions were seen on the vaginal mucosa. Ultrasonography showed a single live fetus corresponding to 36 weeks' maturity with mild intrauterine growth retardation. The results of a nonstress test were negative. Her hemoglobin was 10.2 g/dL. Tests for syphilis and human immunodeficiency virus were negative.

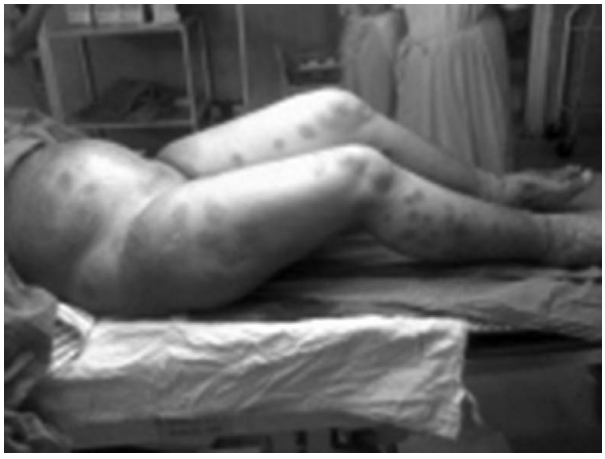

Figure. Clinical photograph showing lesions over the abdomen and lower limbs.

Based on the findings of intrauterine growth retardation, decreased fetal movements and negative nonstress test, the patient underwent emergency lower segment cesarean section under general anesthesia. A 2.35-kg baby boy was born with a normal Apgar score and no evidence of skin lesions.

New, less severe lesions appeared on the patient's body and older lesions started crusting from the third day of puerperium. The baby had no such lesions and was fully immunized. The patient did not breastfeed the baby because of the lesions on her breast, even though there were no other contraindications for breastfeeding. The baby was fed cow's milk. The patient

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remained in hospital for 10 days. Steroids were continued during the puerperium and were slowly tapered after 6 weeks.

HG is an autoimmune disease and may be associated with other autoimmune diseases, such as Graves disease, vitiligo and alopecia areata. It is a disease unique to pregnancy, which usually starts with pruritic papular and urticarial eruptions on the abdomen, and then spread to other flexural areas of skin. Generalized bullous eruptions rapidly ensue, which may affect the palms and soles. Facial and mucosal involvement, as was seen in our patient, is rare. HG is generally seen in the second or third trimesters of pregnancy, although the disease has been reported as early as during the first 2 weeks of gestation in rare cases. In our patient, lesions first appeared in the third trimester. In most instances, HG patients are effectively treated during the early stages of the disease, and the pregnancy usually ends with normal labor. Most patients improve following delivery, and the skin eruptions gradually disappear. Several authors have documented recurrences of the disease in subsequent pregnancies [7,8], and interestingly, the disease may increase in severity with each pregnancy. An uninvolved or skipped pregnancy following a previously affected pregnancy is seen in approximately 8% of HG patients [9]. Recurrences associated with menses or ovulation, or with the subsequent use of oral contraceptives, have also been reported. HG is not associated with maternal risks other than an increased risk of Graves disease, although there have been reports of miscarriages and an increased frequency of premature deliveries with low birth weight newborns [10]. On rare occasions (1 in 100,000 pregnancies), similar lesions can develop in neonates, but these are transient and gradually disappear during first 2 or 3 days of life without any treatment [11,12]. Infants of mothers treated with oral steroids should be monitored for evidence of adrenal insufficiency. No increase in fetal morbidity or mortality has been documented, except for one case of fetal cerebral hemorrhage.

The histologic features of HG are characterized by the detachment of the epidermis from the dermis and by an intense inflammatory infiltrate rich in eosinophils and neutrophils in the upper dermis. HG appears to be mediated by autoantibodies specific for the hemidesmosomal glycoprotein BP-180. Provost and Tomasi [13] reported that HG was characterized by linear deposition of complement C3 along the cutaneous basement membrane zone (BMZ) of perilesional skin, demonstrated by direct immunofluorescence. They also reported that the serum of these patients contained "HG factor" (a complement-fixing anti-BMZ IgG1 antibody, identified by indirect immunofluorescence test). Demonstration of C3 deposition along the BMZ by direct immunofluorescence is accepted as the gold standard for the diagnosis of HG.

HG should be differentiated from other dermatoses of pregnancy, especially pruritic urticarial papules and plaques of pregnancy, allergic contact dermatitis, and drug eruptions. A careful history and clinical examination are usually sufficient to rule out allergic contact drug eruptions and preexisting bullous disease with flare during pregnancy. Accurate differentiation between HG and pruritic urticarial papules and plaques of pregnancy has important implications for fetal and maternal prognosis. Immunofluorescence studies are the best way of making this differentiation.

The first-line treatment of HG, especially in advanced lesions, is systemic corticosteroids at a dose of 0.5 mg/kg/day of prednisolone. The daily dose should not exceed 80 mg, except in rare circumstances when the condition is severe, where 180 mg/day has been used. Some authors have suggested increasing the steroid dose for a short time during the early postpartum period to prevent exacerbations. Early urticarial lesions may respond to topical corticosteroids, as well as to oral antihistamines. Alternative medications are dapsone, sulfapyridine, pyridoxine, and cyclosporine. Refractory cases of HG respond better to adjuvant medications, such as methotrexate, azathioprine, gold, pyridoxine and cyclosporine, especially in the postpartum period. However, their use is limited to patients who are not breastfeeding. Early delivery may be warranted in refractory cases. One report also indicated some benefit from minocycline in a case of postpartum HG [14].

Plasmapheresis or chemical oophorectomy with goserelin has also been used for recalcitrant HG with some success. Plasmapheresis should be considered in patients who fail to respond to high doses of oral steroids, or when oral steroids are contraindicated [15].

High-dose intravenous immune globulin combined with cyclosporine has been used to treat HG with some success [16]. Based on the possibility that autoantibodies and T cells from HG against BP180 antigens may be involved in the pathogenesis of the skin lesions, it is hypothesized that new therapies could involve the interruption of T- and B-cell activation upon exposure to BP180 peptides, thus rendering the patient tolerant to this antigen.

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