Review on Pemphigoid Gestationis

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DEFINITION

Pemphigoid gestationis (PG), previously known as herpes gestationis, is a rare intensely pruritic autoimmune blistering condition occurring during pregnancy and puerperium. It has been reported in association with hydatidiform mole[1,2] and choriocarcinoma.[3]

INCIDENCE

Kolodny counted the number of cases over 18 years in two hospitals in St. Louis and found only two among 112,769 pregnancy cases, this gives an incidence of 1:50,000 to 1: 60,000 pregnancies.[4]

CLINICAL FEATURES

Pemphigoid gestationis may begin during the first or any subsequent pregnancy. It may develop between 9 weeks of gestation and one week postpartum, but most frequently it presents during the second and third trimesters.[5] Although few patients experience less trouble during succeeding pregnancy,[6,7] the condition is most likely to recur in subsequent pregnancies, usually with an earlier onset and more severe disease.[5,8]

Occasionally, subsequent pregnancies may not be affected. Such skipped pregnancies are more likely to occur following a change in paternity or when the mother and fetus are fully compatible at the HLA-D locus.[9] When the eruption begins in the mid trimester there is usually a period of relative remission in the last few weeks of pregnancy, followed by an abrupt flare immediately after delivery. Shornick et al reported that post-partum exacerbation occurred in 31 out of 42 involved pregnancies and usually within the first 12-48 hours.[7] The average duration post-partum was 4 weeks for bullous eruption and 60 weeks for urticarial lesions. There are reports of cases with clinical activity persisting for more than 10 years.[10,11]

The onset is typically gradual, but may occasionally be explosive. The lesions at onset consist of severe pruritic erythematous urticated papules and plaques which become target like, annular, or polycyclic wheals. After a few days to a month, vesicles develop and gradually enlarge to become tense bullae. In 81% of cases the lesions begin on the abdomen around the umbilicus.[5] Other commonly affected sites are the thighs, palms and soles.[5] When fully developed the eruption may involve virtually any other area, but the face and oral mucosa are only rarely involved.[5] When the bullae or vesicles rupture, denuded areas become covered with a brownish yellow or haemorrhagic crust. If secondary bacterial infection or severe excoriation does not occur, healing usually proceeds without scar formation, but post inflammatory hyperpigmentation is not unusual.[12] Malaise, fever and chills may occur during a severe eruption.

HISTOPATHOLOGY

The histopathology of the early urticarial lesion of PG demonstrates epidermal and papillary dermal edema which if intense, results in tear drop appearance.[13] There are also occasional foci of eosinophilic spongiosis. In the dermis there is a perivascular infiltrate composed of lymphocytes, histiocytes, and frequently eosinophilis. The bullae are subepidermal and they invariably contain numerous eosinophilis.[14] Ultrastructural studies of PG have demonstrated focal degenerative changes in epidermal cells leading to cellular necrosis of basal cells. The destruction of cell membranes appear limited to the dermal side of the basal cell. Blister formation occurs within the lamina lucida between necrotic epidermal cells and lamina densa.[15] However, all these histological features are not diagnostic.

DIAGNOSIS

The precise diagnosis of the disease relies on immunopathological studies. Direct immunofluorescence usually reveals in-vivo bound complement (C3) in a linear pattern at the basement membrane zone (BMZ) . This occurs in perilesional and clinically normal skin in all patients with PG .[16] Immunoglobulin G deposits are sometimes present at the same site in only about 25% of cases. The exact site of immunoreactant deposition can be determined by pretreatment of skin with molar sodium chloride, which separates the tissue into epidermis and dermis at the level of lamina lucida. Using this chemically split skin as a substrate for indirect immunofluorescence, the antigen recognised by the sera of patients with PG is localised to the epidermal aspect of the split.[16]

A circulating serum factor termed pemphigoid gestationis factor, which is a complement binding IgG, can be detected by the complement-fixation immunofluorescence technique using normal human skin as substrate.

Nowadays indirect assay using more specific and sensitive monoclonal antibodies against IgG subclasses reveals that all patients with PG have circulating IgG antibodies directed against the cutaneous basement membrane. In-vivo deposition of immune reactants may also be detected in the placenta of patients with PG. Immunoglobulin (usually IgG1) and complement are deposited in a linear band along the amniotic basement membrane.[18] The complement or IgG deposits are occasionally demonstrable for months to years after all clinical evidence of disease has resolved. Thus direct immunofluorescence remains a powerful diagnostic tool in patients who have already been treated, or even for those in whom all clinical signs of disease have resolved. Correct diagnosis is important to predict potential recurrence during future pregnancies. Thus the condition can be diagnosed and treated earlier in a subsequent pregnancy, or patients may choose definitive procedures for birth control when faced with the possibility of recurrent disease.

Differential diagnosis

The main differential diagnosis is polymorphic eruption of pregnancy (PEP) which occurs later in the third trimester of pregnancy. The skin eruptions in PEP usually begins at the striae, although vesicles may appear they almost never become bullous. In PG the neonate may have similar skin involvement as the mother, which is an useful distinguishing feature from PEP. Finally, immunofluorescence is the most definitive means for differentiating the two conditions because it is consistently negative in PEP.

ETIOLOGY AND PATHOGENESIS

Autoimmunity

Pemphigoid gestationis is an autoimmune disorder triggered when women with susceptibility to high immune responsiveness are exposed to antigenic factors derived from their sexual consorts.[19] Maternal human lymphocytic antigen (HLA) studies have revealed a significant increase in A1, B8, and DR3 in patients with PG.[9,17] These antigens demonstrate linkage disequilibrium. Among these haplotypes DR3 is probably the most important etiology in inducing an increase in immune responsiveness. In a study of 25 patients with PG, Holmes et al found that 80% got the HLA antigen DR3.[9] They also found an increase in frequency where DR3 occurred in combination with DR4. Shornick et al also noted 43% of PG patients had this phenotype, compared with 31% of normal controls. This suggests that the presence of DR4 also confers an increase in immune susceptibility and patients with HLA-DR3 and DR4 are particularly prone to develop immune associated disease. It has been speculated that paternal antigens might play a role in pathogenesis of PG. Supporting this is the fact that in some patients with pregnancies by several consorts, onset of PG has coincided with a change in partner.[9]

Since a fetus is not required for a women to develop disease, the production of PG must somehow be related to the presence of a placental factor. The disease may be triggered by the maternal immune system recognizing a placental antigen which cross reacts with the patient's skin.[16] This may explain why PG so often begins at the periumbilicus. In fetal life the skin at the umbilicus is in continuity with the chorio-amniotic membrane covering the umbilical cord, therefore in adult life there may be cells in this region which retain some of their chorio-amniotic antigenicity.[9]

PG represents an unique situation amongst disease in which aberrant MCH class II expression is seen. It

has been shown that when by chance or by altered paternity, the mother and fetus have identical HLA-D phenotypes, unaffected or skipped pregnancies occurred. The affected pregnancies in these women occurred when there were differences between mother and fetus at the HLA-D locus. The allogenic effect in these cases was important in determining the occurrence of the disease.[20]

Effect of hormones

The known exacerbation with delivery, menses, oral contraception, and the occurrence of PG in association with hydatidiform mole and choriocarcinoma strongly suggest that hormones play a significant role in the aetiology of PG.

In a report by Holmes et al, oral contraceptive was prescribed for 8 patients with a history of PG. In 4 patients this produced clinical relapse.[9] The oestrogen component of oral contraceptive is primarily responsible for exacerbation. There is experimental evidence that in certain concentrations, oestrogen may have immuno-enhancing properties and this may account for its effect in PG.[21] Progesterone has been shown to have immunosuppressive effects similar to glucocorticoids, so it should exert an inhibitory effect on PG. The effect of progesterone could also account for the changes in severity that occur during pregnancy. In the last few weeks of pregnancy when progesterone levels are high, PG tends to be in relative remission. It then tends to flare in post-partum coinciding with an abrupt fall in progesterone levels.

THE ANTIBODY IN PG

1. PG factor

Kelly et al found that PG factor was an IgG1autoantibody. It was detected in 100% of sera examined from 30 patients with PG.[18] Holmes et al stated that if PG factor was of pathogenic importance, one expects clinical remission post-partum would coincide with disappearance of anti-BMZ antibodies; but this was not the case in their patients, as IMF had remained positive after cessation of clinical activity.[9] Moreover, PG factor titres bore no relationship to clinical activity. In contrast to this, another report studied serial serum samples in one patient, showing disappearance of PG factor from serum at 5 month postpartum together with resolution of skin eruption.[22] A feature of PG which supports the role of PG factor is the occurrence of neonatal PG with positive direct IMF.[23] As PG factor is an IgG, it will cross the placenta in all cases and if it were pathogenic, neonatal involvement should be common. However, PG lesions are reported in only about 5% in infants born to mothers affected by PG.[24] Thus the role of PG factor in pathogenesis of PG is still uncertain.

2. Anti-HLA antibodies

Shornick et al reported that cytotoxic anti-HLA antibodies were found in all women with a history of PG.[25] In 98% of cases, the antibodies was against class I antigen and 25% was against class II. The presence of these antibodies, together with the production of anti-basement membrane zone antibodies is a further support for an immunological basis in this disease. There was increase frequency of HLA-DR2 in husbands of patients who developed PG, and this increase was even more pronounced when the patient has the DR3 and DR4 combination.

THE ANTIGEN IN PG

Indirect immunofluorescence studies using chemically (1 Molar NaCl) separated skin as substrate have localised the antigen to the epidermal aspect of the cleaved tissue on the lower pole of the basal keratinocyte, a binding site similar to that of bullous pemphigoid (BP) sera.[16] A study done by Kelly et al using immunoblotting techniques showed that in PG, the major antigenic determinant recognised by a significant proportion of patients' sera is a macromolecule of 180 kD.[26] This major PG antigen molecule can be extracted from normal epidermis and is a normal constituent of skin. Some PG sera also bound to the major antigen in BP, a 230 kD protein. Similarly, some BP sera bind to the major PG antigen in addition to the BP antigen. Therefore there is some degree of shared molecule specificity between the two conditions.

In a recent study by Kelly et al, it was shown that the autoantibodies thought to be pathogenic in PG adhere to isolated basal keratinocytes.[27] This suggests that the antigen is an integral part of the basal keratinocytes rather than an extracelluar matrix component of lamina lucida of epidermal basement

membrane. Unlike bullous pemphigoid where the pattern of antibody binding is in a polar distribution, in PG two distinct patterns of antibody binding are seen. In a proportion of patients there was a similar polar distribution to that seen in BP; while in just over half of the patients the pattern of fluorescence was uniform around the cell periphery.

RELATIONSHIP BETWEEN PEMPHIGOID GESTATIONIS AND BULLOUS PEMPHIGOID

There are many similar features between PG and BP. Clinically, both disorders are characterised by pruritic urticarial lesions which develop into large tense bullae. They are both responsive to systemic corticosteroids. Histopathologically both demonstrate subepidermal bullae containing numerous eosinophils. Immunofluorescence shows that C3 is deposited at the BMZ of lesional skin in both disorders. Immunoelectron microscopy performed with a peroxidase antiperoxidase sandwich technique, revealed the in-vivo binding of IgG at the lamina lucida with identical distribution pattern. PG and BP share the same antigen determinants, 180 kD and 230 kD molecules; while antibodies against the 180 kD antigen are prevalent in PG, antibodies against the 230 kD antigen are more frequent in BP.

However, the age of onset and the distribution of lesions are different in BP and PG. BP is a disease confined mostly to the elderly, whereas PG occurs exclusively in women of child bearing age and shows invariable association with pregnancy. While PG frequently begins near the umbilicus and commonly remains confined to the abdomen and thigh, the distribution of lesions in BP is often generalised. The clinical activity of PG may be affected by oestrogen or progesterone, but there is no evidence that BP is hormonally modulated. Furthermore, PG and BP differ immunogenetically. In PG there is a significant increase in frequency of HLA antigen A1, B8, DR3, and a combination of DR3 and DR4; whereas in BP the frequencies of HLA antigens are normal.[17] Using monoclonal antibodies, the PG factor was found to be an IgG1 anti-basement membrane antibody, however the BP IgG subclass was heterogeneous with IgG4 being the dominant isotype.

Associated autoimmune disease in PG

Shornick et al determined the frequency of other autoimmune diseases in 75 patients with history of PG. The results showed an increased frequency of Graves disease (11%). They also found these patients had increased risk of developing other auto-antibodies, such as gastric parietal cell antibodies and thyroid microsomal antibodies. There was also an increased frequency of autoimmune disease in family member of patients with PG. They concluded that associated autoimmune disease in PG is unusual but does occur, the most frequent was Graves disease.[28]

Maternal and fetal risk

Maternal morbidity parallels the severity, duration, and complications (usually infectious) of PG. Steroid therapy effectively suppresses this morbidity.

Shoenick et al (1983) suggested that literature reviews were biased towards the more severely affected cases, and in their study of 28 patients they studied the outcome of 50 pregnancies affected by PG. They assessed fetal risk by measuring the infants weight and compare with the weight expected for the gestation. They reported an increased frequency of low birth weight and small-for-gestational age babies in those pregnancies affected by PG.[7]

A recent study by Shornick et al specifically addressed the issue of fetal risk in a larger group of women with PG. They found no increased rate of spontaneous abortion or significant mortality, but did demonstrate an increase incidence of prematurity and a slight increase in small-for-date babies associated with PG. The use of systemic steroids did not appear to influence risk.[29] As patients with PG have evidence of abnormal immune reactions within their placental villi, clinical evidence of placental insufficiency might be expected. Their finding of prematurity and low birth weight is compatible with low grade placental dysfunction.

Infants with bullous lesions resembling PG have been reported, this has been attributed to passive transfer of the mother's anti-basement membrane zone antibodies across the placenta.[23] Clinical symptoms appear at birth or within several days after birth, with spontaneous regression within three weeks without recurrence. Because of its low molecular weight, the

PG factor which is an IgG1 can cross the placenta. It can be demonstrated in the serum of neonate whom it can induce lesions similar to those of the mother. It is perhaps surprising that neonates are so rarely affected. Clinically apparent skin disease occurs only in about 2%-5% of new-born infants. Shornick reported a higher percentage of neonates having subclinical disease, as determined by positive immunofluorescence findings.[6] The lesions in the new-born are generally mild; they often take the form of an erythematous or erythemato-papular rash;[4,23] but rarely frank bullous lesions occur.

Treatment

Mild cases can be managed with topical steroids and oral antihistamines. The treatment of choice for more severely affected patients is systemic steroids. However, there is no disadvantage in withholding systemic corticosteroids until it is certain that they will be required.[19] There is invariably a response to a dose of 40 mg prednisolone daily, and this can usually be reduced fairly rapidly to a daily maintenance dose of 10 mg. Although PG is well known to undergo spontaneous improvement after delivery, the immediate post-partum period may be a time of peril, as post-partum flare occurs frequently. It is worth anticipating this by increasing the dose temporarily. Lawley et al reported that there was no significant difference in the rate of uncomplicated life deliveries in a group of patients treated with systemic corticosteroids compared with a group treated with topical corticosteroids.[30] However, those patients requiring systemic corticosteroids may represent a group with more severe maternal disease and greater fetal risk. Therefore the possibility exists that without systemic corticosteroid therapy, there might have been an even higher rate of fetal morbidity and mortality. It has been reported that low dose systemic steroid in the second and third trimester of pregnancy did not appear to be associated with an increased risk of congenital abnormality, though the mother must be carefully monitored for the development of diabetes and hypertension.

If the condition does not respond to corticosteroids or if they are contraindicated, plasmapheresis should be considered.[31] The use of plasmapheresis, however, is limited by logistics and expense; and the effect may be temporary.

In 1984 MacDonald reported a case of severe PG being treated successfully with Ritodrine, which is a beta-mimetic drug and predominantly a beta-2 agonist.[32] It is usually prescribed for patients in premature labour to reduce uterine contractility.

Other treatments that have been tried in PG include pyridoxine; out of five patients treated by Holmes et al, only one showed any evidence of improvement.[19] Dapsone is unhelpful and it is now contraindicated because it can cause haemolytic disease of the new born.

In a recent report by Garvey et al, Goserelin, a new luteinising hormone releasing hormone (LHRH) agonist, was used in a severe long standing case of PG. A chemical oophorectomy was induced using this LHRH agonist, with complete remission within 6 months of initiating this treatment.[33] However, this treatment is contraindicated during pregnancy.

CONCLUSION

Although PG is a rare bullous disorder in pregnancy, accurate diagnosis can be made with the advance in immunofluorescence study. Once the diagnosis of PG has been made, precautions can be taken in the subsequent pregnancy or the patient can choose effective means of birth control to prevent its recurrence.

Learning points:

The lesions in pemphigoid gestationis most often start around the umbilicus during the second and third trimester, whereas those in polymorphic eruption of pregnancy usually begins at the striae of abdomen in last trimester. Neonate of a mother with blistering disorder in postpartum period should also be examined.

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