New Observations on Pemphigoid ‘Herpes’ gestationis

M.M. Black

Department of Dermatopathology, St. Johns Institute of Dermatology, St. Thomas’ Hospital, London, UK

Key Words
Pemphigoid gestationis
Bullous disorder
Immunofluorescence
Immunogenetics

Abstract
Pemphigoid gestationis (PG) is a rare auto-immune bullous disease of pregnancy that is characterized by linear deposition of C3 along the basal membrane zone of lesional, perilesional and uninvolved skin when examined by direct immunofluorescence. Circulating antibodies of IgG1 class are also present. The aberrant expression of MHC class II molecules in the placenta appears to be important in triggering the immune response in the lamina lucida of the basement membrane zone in the placenta which then cross-reacts with the skin. PG appears to be unique in that it produces both basement membrane zone antibodies and anti-HLA antibodies. Chronic placental insufficiency can occur so that there is a clear tendency for premature deliveries and small-for-date babies. Secondary autoimmune disorders are significantly increased in PG and appear to be related to the HLA antigens DR3 and DR4. Finally abnormalities of complement polymorphism have recently been described.

Martin M. Black, MD, FRCP, FRCPath, Department of Dermatopathology, St. Johns Institute of Dermatology, St. Thomas’ Hospital, London SE1 7EH (UK)

Pemphigoid gestationis (PG) is a rare auto-immune bullous disease occurring during pregnancy and the puerperium or occasionally in association with trophoblastic tumours [1]. It is estimated to occur in 1 in 40,000 pregnancies [1]. We have been fortunate to have established a National Register for PG within the St. John’s Institute of Dermatology in London. So far we have collected about 80 cases, and this has given us the opportunity to investigate in depth this very rare bullous condition.

Clinical Features
PG may develop between 9 weeks gestation and 1 week post partum but most frequently presents between the 2nd and 3rd trimester. Characteristically it recurs and usually worsens in subsequent pregnancies, but ‘skipped’ pregnancies rarely occur. The disease often flares abruptly after delivery and is capable of lasting many months or even years. Early lesions are pruritic erythematous urticated plaques which may become annular or polycyclic. Gradually vesicles or larger bullae appear so that ultimately the clinical picture strongly resembles bullous pemphigoid. A useful diagnostic feature is that the eruption usually begins in the peri-umbilical area before spreading to involve the abdomen, thighs, palms and soles.

Histology and Immunofluorescence
The histological features are not diagnostic, but usually marked oedema and tissue eosinophilia are associated with eosinophilic spongiosis and subepidermal separation. Direct immunofluorescence reveals linear C3, basal membrane zone deposition in all active cases and is a critical criterion in establishing the diagnosis. Circulating antibodies are often present and are
of IgG1 class. Transplacental passage of antibody occurs and can result in neonatal disease, which is milder and transient in nature.

**Differential Diagnosis**

The principal pregnancy dermatosis which may closely resemble PG is polymorphic eruption of pregnancy [2]. It is much more common than PG, frequently involves stretch striae and is a milder disease. The principle distinguishing feature is that direct immunofluorescence in polymorphic eruption of pregnancy is always negative.

**Treatment**

Systemic corticosteroids are the mainstay therapy in suppressing bullous lesions in PG. A good response is usually obtained with a dose of prednisolone 40 mg daily which can then be gradually tapered. Unfortunately dap-sone, methotrexate, cyclophosphamid or azathioprine are essentially contra-indicated in pregnancy and even when used post partum are usually ineffective. Goserelin, a new luteinizing-hormone-releasing hormone, has recently proved useful in severe, long-standing PG [3]. The treatment produces a reversible chemical oophorectomy but is clearly contra-indicated in the pregnant patient with PG.

Recent observations in our unit into PG have concentrated on the following areas. Other auto-immune diseases were noted, e.g. vitiligo, ulcerative colitis. An increased frequency of auto-immune diseases in family members of patients with PG was also found. This secondary auto-immune association in PG appears to be related to the prevalence of HLA-DR3 in the condition.

**HLA Class III associations in PG**

Shomick et al. [6] studied 48 patients with PG for complement polymorphisms, encoding C2, factor B, C4A or C4B. The principal surprise finding was that 90% of the PG cases carried a C4 null allele, suggesting that the C4 null allele could be the primary genetic association in PG. This observation could explain the impaired handling of circulating immune complexes and auto-antibodies that are a characteristic feature of the condition.

**Fetal prognosis**

The risks to the fetus or neonate in PG have historically been controversial, principally because few studies were large enough to evaluate the problem. Shornick and Black [4] reported a series of obstetric histories in 74 women with PG and were able to compare a nearly equal number of PG pregnancies to ‘normal’ pregnancies in the same women. The results clearly indicated a significant increase in premature deliveries in the PG group as well as a tendency to small-for-date babies. These findings would be compatible with low-grade placental dysfunction in PG.

**Anti-HLA Antibodies in PG**

Shornick et al. [7] have recently studied 39 cases of PG for the presence and specificity of anti-HLA antibodies. Anti-HLA antibodies were universally found. Specificity was against class I antigens in 98% and class II antigens in 25%. Almost all anti-HLA antibodies were cytotoxic. The universal presence of anti-HLA antibodies in PG, together with the production of anti-BMZ antibodies is a further indication of an immunological basis for the disorder.

**Unresolved Issues**

Secondary Auto-Immune Diseases in PG
Shornick and Black [5] studied 75 patients with PG and determined the frequency of associated auto-immune diseases.

Clearly PG is a unique auto-immune disease that has profound potential clinical implications to the fetus and mother. We are still not certain what the primary event is in the pathogenesis of PG. Further work needs to be undertaken on the exact molecular nature of the PG antigen and 11% had Graves’ disease (thyrotoxicosis), and a scattering of its full relationship to the bullous pemphigoid antigen.

References
51