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Pemphigoid gestationis: Toward a better understanding of the etiopathogenesis

Christian D. Sadik, MD*, Ana L. Lima, MD, Detlef Zillikens, MD

Department of Dermatology, Allergy, and Venereology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany

Abstract Pemphigoid gestationis (PG) is the only autoimmune disease exclusively emerging in pregnancy. It belongs to the pemphigoid group of disorders, a class of autoimmune blistering skin diseases featuring an immune response against different hemidesmosomal proteins. PG is caused by a break of immunotolerance against the hemidesmosomal protein BP180. Several lines of evidence suggest that this break of immunotolerance is linked to specific maternal major histocompatibility complex (MHC) class II gene variants and aberrant expression of MHC class II molecules in the placenta. The close time association of the emergence of PG with pregnancy and the obviously very short period required from the initial break of immunotolerance to the onset of skin inflammation set PG into a unique position among autoimmune diseases in view of the fact that, for other autoimmune diseases, the time and site of the break of immunotolerance are usually vastly elusive and the period of silent disease can only be speculated on. In this review we highlight the features of PG and summarize current knowledge about its pathogenesis. We believe that this disease offers the best opportunity to elucidate comprehensively all phases of the pathogenesis of an autoantibody-driven disease.

Introduction

Pemphigoid diseases are blistering autoimmune diseases of the skin and mucous membranes. These diseases feature an autoantibody-driven immune response against different components of the hemidesmosomal complex, which is implementing the adherence between dermis and epidermis.[1] The disease pemphigoid gestationis (PG) is unique among these diseases in that it, in the vast majority of cases, exclusively affects pregnant women, thus associating pregnancy and its concurrent immunologic alterations with a break of tolerance against the hemidesmosomal protein BP180, which finally precipitates the immune response in the skin.[1] This autoimmune pathogenesis is adequately reflected in the disease designation *pemphigoid gestationis*, which has replaced the previous designation *herpes gestationis,* coined in 1872, which referred to the meanwhile refuted hypothesis that a herpesvirus infection may cause the disease.[2]

Epidemiology and clinical presentation

PG has an estimated incidence of 1 in 20,000 to 50,000 pregnancies.[1,3,4] In a small number of cases, the disease can be a paraneoplastic manifestation of trophoblastic tumors, hydatidiform mole, or choriocarcinoma.[5,6] It sometimes relapses with the onset of menses or use of oral contraceptives postpartum but quickly remits after their discontinuation.[4,7,8] In PG, an immune

* Corresponding author. Tel.: +49 451 500 1760; fax: +49 451 500 5161.
E-mail address: Christian.Sadik@uni-luebeck.de (C.D. Sadik).

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response against the hemidesmosomal protein BP180, also designated as type XVII collagen or BPAG2, is executed. The disease starts between the second trimester and puerperium and manifests with severe pruritus and inflammatory skin lesions. Pruritus can emerge before the skin lesions and can remain the only symptom. Erupting skin lesions are polymorphic and can include erythematous papules and plaques, erythema multiforme–like or eczematous lesions, papulovesicles, and bullae (Figure 1, A-D). In many cases, however, the typical blisters do not develop, because the duration of disease, which is usually terminated quickly after delivery, is often too short for skin lesions to progress into the bullous stage.[1] Skin lesions usually first erupt around the umbilicus and subsequently spread to the abdomen and the extremities. The disease involves the face and mucous membranes only rarely.[9] Occasionally, concomitant general symptoms, such as fatigue, subfebrile temperatures, shivers, and stress, occur.

PG is mostly self-limiting, and symptoms usually completely disappear by 6 months postdelivery[4]; however, it recurs in 90% of all cases in subsequent pregnancies and often with aggravated severity.[4] Intriguingly, the risk for re-emergence of PG in subsequent pregnancies has been suggested to be distinctly lower when the consort changes.[4] In less than 5% of cases, PG becomes chronic and, thus, indistinguishable from bullous pemphigoid.[4,10]

PG is not significantly associated with other autoimmune disease except for hyperthyroidism (Graves disease), from which 10-11% of PG patients suffer compared with 0.4% of the general female population.[4,11] The disease can also affect the fetus, with a slightly increased risk for prematurity and small–for–gestational age babies reported.[12] Early PD onset in the course of pregnancy, as well as frank blister formation, are associated with a higher risk of these adverse outcomes. In addition, 10% of newborns exhibit typical PG skin lesions caused by passive transfer of maternal immunoglobulin G (IgG).[10,13]

Pathogenesis

The pathogenesis of PG is still largely elusive and, in contrast to what was previously anticipated, is not linked to a viral infection. PG has a strong association with the maternal HLA-DRs DRB1*0301 (HLA-DR3), found in 61-80% of PG patients but only 22% of controls, and DRB1*0401/040 X (HLA-DR4), present in 52% of PG patients and in 33% of controls. Notably, the combination of these two HLA haplotypes is found in 45% of PG patients and in only 3% of controls.[14,15] This strong association indicates a pivotal role of MHC class II in the pathogenesis of the disease.[10] MHC class II molecules are aberrantly expressed on amniochorionic stromal cells and on the trophoblast. This aberrant expression is presumably involved in a loss of immunoprivilege of the fetoplacental unit. As a consequence, BP180, which is expressed in the amniotic epithelium of the placenta and the umbilical cord,[16,17] is presented to maternal MHC class II in the presence of paternal MHC class II and is recognized as a foreign antigen, resulting in the formation of IgG autoantibodies, predominantly of the IgG_1 and IgG_3 subclasses,[1,18–22] directed to BP180. In addition, this direct contact between the maternal and paternal immune systems also causes the formation of antibodies against paternal MHC I antigens. These autoantibodies are detected in all PG patients but in only 25% of healthy multiparae.[23] A conclusive pathogenic role for these anti–MHC-I antibodies has not been revealed. These autoantibodies bind to the amniotic membrane and have been hypothesized to be the result of an immunologic insult against placental antigens during gestation. Binding of these antibodies to the basal membrane zone of the placenta is accompanied by local infiltration with lymphocytes. The placental basement membrane of PG patients exhibits slight structural alterations with a deficit in the development of hemidesmosomes in the trophoblast basal areas and partial detachment of basement membranes from the trophoblasts, which is in line with proceeded immune response. Despite these structural changes, the placenta does not exhibit functional deficits.[24]

The break of immunotolerance in the placenta eventually leads to the generation of IgG autoantibodies against BP180. Its extracellular portion of the 16th noncollagenous (NC16 A) domain is the immunodominant region (Figure 2) with IgG autoantibodies directed to the NC16 A domain formed in 90%

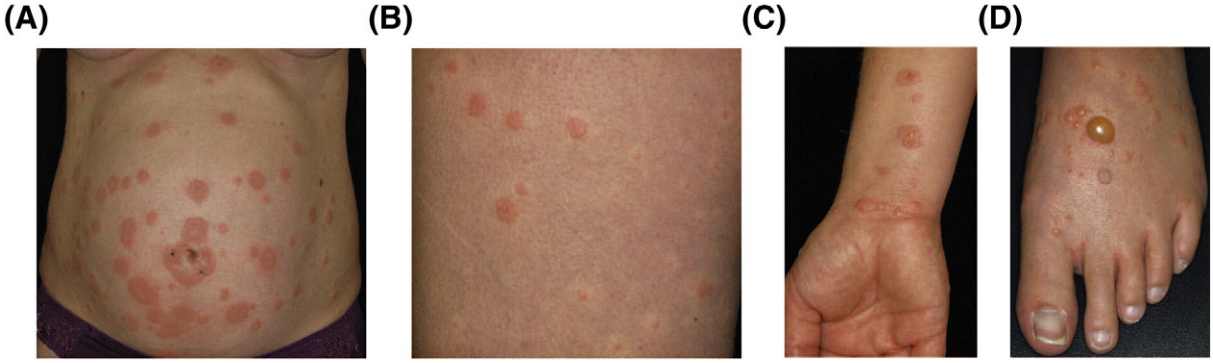

Fig. 1 Clinical presentation of pemphigoid gestationis. Typical presentation of pemphigoid gestationis patients with (A) skin lesions around the navel; (B) urticarial papules; (C) small skin blister on urticarial papules; (D) massive, tense skin blisters.

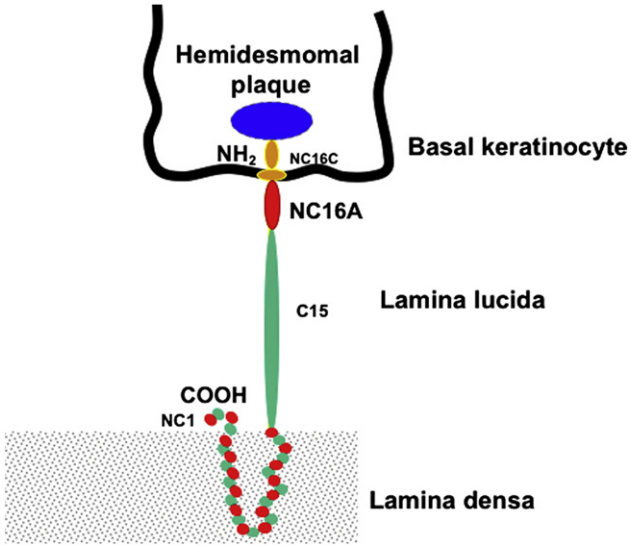

Fig. 2 Schematic diagram of the structure of BP180. BP180 connects the lamina lucida with the hemidesmosomal plaque in the inside of the basal layer keratinocytes. The immunodominant domain of BP180 in pemphigoid gestationis is the NC16 A domain, which directly neighbors the basal keratinocyte's cell membrane.

of all PG patients.[1,18–22] Although the ectodomain of BP180 is shed into the amniotic fluid, leaving behind the juxtamembraneous N-terminal proportion of NC16 A, no autoantibodies against this part of BP180 are formed in PG patients, confirming that the relevant antigenic proportion of BP180 in PG is solely restricted to the N-terminus of the extracellular domain of BP180.[25]

Another factor contributing to the emergence of PG is possibly an aberrant complement system, with 90% of PG patients carrying the C4 null allele (C4*QO), in contrast to 43% of controls. This may impair the removal of immune complexes and may facilitate their deposition[26]; however, the C4 allele is closely located at the DR alleles on chromosome 6, which consequently leaves a strong disequilibrium, complicating the ability to discern the primary genetic link in PG relevant for disease pathogenesis.

In addition to the placenta, BP180 is expressed in the skin and in the central nervous system. In the skin, it serves as hemidesmosomal transmembrane glycoprotein protein BP180, which is essential for dermal-epidermal adhesion. Accordingly, anti-BP180 autoantibodies are deposited at the dermal-epidermal junction (DEJ), where they activate complement and presumably other molecular mechanisms, which finally initiate the recruitment of effector cells, predominantly eosinophils but also neutrophils, to the DEJ. There, these cells are activated and subsequently degranulate.[27] The degranulation products, among them proteases, are presumably responsible for the physical detachment of dermis and epidermis, yielding skin blisters and erosions.[28,29]

Another layer of complexity is added to the pathogenesis of PG by the modulatory effects of hormones on disease activity.[8,30] The course of disease apparently correlates to the levels of progesterone and estrogens. Disease activity usually declines toward the end of the pregnancy, when progesterone levels are high, and then increases immediately postpartum, when progesterone levels decrease and estrogen levels rise; likewise, progesterone levels decrease premenstrually, when PG can potentially flare.

Diagnosis

In addition to the typical clinical phenotype, histopathology and direct and indirect immunofluorescence microscopy as well as ELISAs and BIOCHIP assays can be used to corroborate the diagnosis PG. These laboratory diagnoses are often required to distinguish PG from other itching dermatoses of pregnancy, especially from polymorphic eruption of pregnancy (PEP), which often presents clinically with an identical picture.

Histopathologically, a papillary edema with eosinophilic spongiosis and an inflammatory infiltrate consisting of eosinophils and lymphocytes are typical for PG. In later stages, subepidermal split formation becomes evident. PG can be diagnosed most reliably by detection of IgG autoantibodies and complement deposited at the DEJ in direct immunofluorescence microscopy (Figure 3). Direct immunofluorescence sometimes remains positive even for 6 months to 4 years after clinical remission.[30]

Some centers refrain from biopsying pregnant women and seek the diagnosis of PG by detection of circulating autoantibodies either by a complement-binding test (ie, indirect immunofluorescence on salt-split human skin in the presence of a complement source) or by anti-BP180 IgG autoantibody ELISA. The latter is more sensitive and more specific and also suitable to monitor disease activity because serum levels of anti-BP180 NC16 A IgG correlate with disease severity.[21,31,32] Alternatively, anti-BP180 IgG autoantibodies can be efficiently detected by BIOCHIP technology.[33]

A novel strategy for the diagnosis of PG is the use of C4d immunohistochemistry to distinguish PG from other dermatoses of the pregnancy. It has recently been reported that the detection of C4d depositions at the DEJ is specific for PG among pregnancy-associated dermatoses.[34] C4d is a stable activation product of the classical complement pathways and its deposition at the DEJ reflects the activation of this pathway by anti-BP180 IgG1 autoantibodies binding at the DEJ. The advantage of C4d immunohistochemistry over direct immunofluorescence is that it can be conducted on formalin-fixed, paraffin-embedded tissues; thus, a single skin biopsy is sufficient for both routine histopathologic examination and the detection of C4d depositions at the DEJ.[34]

Therapy

High-potency topical corticosteroids are the therapy of choice for PG, but therapy can be escalated by administering systemic glucocorticoids, such as 0.25 to 0.5 mg/kg prednisolone. The use of immunoadsorption or intravenous

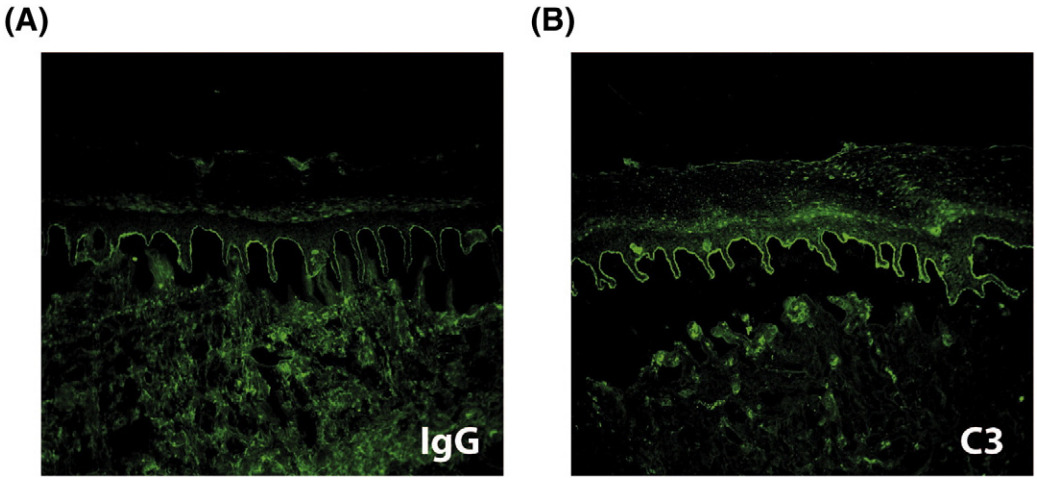

Fig. 3 Direct immunofluorescence of pemphigoid gestationis. Detection of (A) immunoglobulin G (IgG) and (B) complement (C3) deposited at the dermal-epidermal junction.

immunoglobulin has been effective in intractable cases.[35] Intravenous immunoglobulin has occasionally been used in combination with immunosuppressants such as cyclosporine or azathioprine.[36–38] Pruritus control can be achieved with first-generation histamine 1 receptor blockers, such as diphenhydramine and chlorpheniramine, which have a long safety record in pregnant women, but second-generation histamine 1 blockers, such as cetirizine or desloratadine, can also be used.[4]

When PG is still active postpartum, additional treatment options are available in nonbreastfeeding women because the therapeutic restrictions set by the pregnancy no longer apply. Diverse immunosuppressants, including methotrexate, azathioprine, gold, pyridoxine, sulfapyridine, dapsone, and rituximab, can be considered postpartum for treatment of recalcitrant disease.[1,2,4,39–42] The combination of a tetracycline with nicotinamide can also be an effective steroid-sparing option in nonlactating mothers.[43,44]

Conclusions

Although PG is a rare disease and does not pose a major health burden, its pathogenesis was extensively researched before the 1990s. The early investigations associated the emergence of the disease with specific major histocompatibility complex (MHC) class II gene variants and an aberrant expression of MHC class II molecules in amniochorionic stromal cells of the trophoblast. A more detailed understanding of the disease pathogenesis has not been achieved, but it may be instrumental to solving basic research questions on the break of tolerance and the subsequent autoantibody generation.

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