

CASE REPORT

Glucocorticosteroid-resistant pemphigoid gestationis: Successful treatment with adjuvant immunoadsorption

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ABSTRACT

A 40-year old prima para presented with multiple urticaria-like plaques and severe pruritus 2 weeks prior to giving birth by cesarean section. Three days after birth, the disease flared up and tense blisters appeared on hands, lower arms and feet. Based on the clinical presentation, direct immunofluorescence microscopy, complement binding test and detection of high levels of circulating anti-BP180 antibodies, the diagnosis of pemphigoid gestationis was established. Despite treatment with class IV topical corticosteroid and prednisolone p.o. up to 60 mg/day, both skin lesions and severe pruritus progressed accompanied by increasing anti-BP180 antibody serum levels. In order to continue breast feeding, the prednisolone dose could not be further increased and 10 immunoadsorptions over 4 weeks were performed. During this period, skin lesions cleared rapidly, pruritus subsided and BP180-specific serum autoantibodies decreased by 99.5% allowing the reduction of prednisolone to 7.5 mg/day. We conclude that immunoadsorption is an effective and safe adjuvant therapeutic option for severe pemphigoid gestationis.

Key words: autoantibody, bullous, BP180, gestationis, immunoapheresis.

INTRODUCTION

Pemphigoid gestationis (PG) is a rare, autoimmune, subepidermal, blistering dermatosis associated with pregnancy. Its incidence has recently been estimated to be 2.0/1 million inhabitants per year in Germany.¹ The onset is usually during the second and third trimester of pregnancy but may also occur during the post-partum period.² Clinical presentation is characterized by erythematous, pruritic, urticarial plaques on which tense vesicles and blisters may develop.^{3,4} Skin lesions usually arise around the umbilicus and then spread to the mammary region, forearm, thigh, trunk and buttocks, often sparing the face, palms and soles. Mucosal involvement is present in less than 20% of patients.^{2,5}

Pemphigoid gestationis is characterized by autoantibodies to the 180-kDa bullous pemphigoid antigen (BP180) and the extracellular portion of 16th non-collagenous domain (NC16A) has been identified as the immunodominant region of BP180.⁶ Diagnosis is made by the finding of linear deposits of immunoglobulin (Ig)G and/or C3 at the dermoepidermal junction by direct immunofluorescence (IF) microscopy of a perilesional skin biopsy. Serum autoantibodies have a high complement-fixing potential and are traditionally detected by complement binding IF microscopy on human 1 mol/L NaCl-split skin where they stain the epidermal side of the artificial skin.^{7,8} Serum autoantibodies to BP180 can be found in almost all PG patients by western blotting and enzyme-

linked immunosorbent assay (ELISA) using recombinant BP180 NC16A.^{6,9–13} Epitopes on BP180 outside the NC16A domain may also be targeted¹⁴ and in approximately 10% of patients, anti-BP230 reactivity is present.

CASE REPORT

A 40-year-old prima para developed multiple urticarial plaques on the abdomen and legs as well as severe pruritus 2 weeks prior to giving birth to a healthy boy by cesarean section. Three days post-partum, a flare-up occurred with pruritic erythematous papules and urticaria-like wheals spreading to the shoulders and arms. A lesional biopsy of the right upper arm showed a subepidermal split formation with a mixed inflammatory infiltration including eosinophils in the upper dermis. Direct IF microscopy of perilesional skin revealed strong C3 deposits along the basement membrane zone, while staining for IgG reactivity remained negative. Complement binding test by indirect IF microscopy on human split-skin showed staining of C3 at the epidermal side of the split. High levels of serum anti-BP180 NC16A antibodies (initially 100 U/mL; normal <20 U/mL) were detected by ELISA (Euroimmun, Lübeck, Germany) (Fig. 1). No circulating antibodies to BP230 were detected by ELISA (Euroimmun). The patient's human leukocyte antigen (HLA) phenotype DR4, 13(6) DQ8(3) and 6(1) was highly compatible with the clinical and immunopathological diagnosis of PG.

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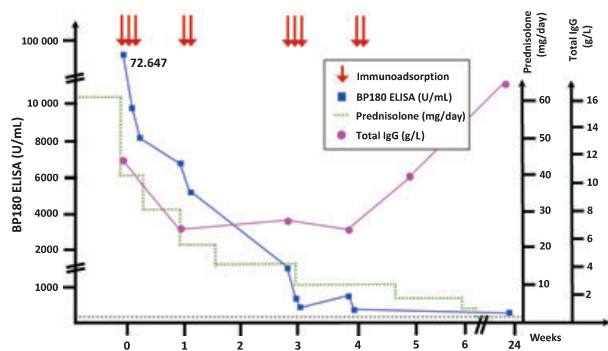


Figure 1. Anti-BP180 NC16A serum autoantibody levels, prednisolone doses and total immunoglobulin (IgG) serum levels prior to and after initiation of immunoadsorption. Enzyme-linked immunosorbent assay (ELISA) levels of serum anti-BP180 antibodies are indicated as blue squares, prednisolone doses by the dotted green line, total serum IgG levels by pink circles (normal values >7 g/L) and immunoadsorption by red arrows. The cut-off level of the ELISA is marked as a dotted black line and the time axis is centered at the initiation of immunoadsorption.



Figure 2. Pruritic erythematous papules and urticaria-like plaques on the abdomen and thighs immediately before immunoadsorption was initiated. Tense blisters arose on the left palm.

Treatment with prednisolone 25 mg/day p.o in combination with lesional application of betamethasone 0.1% ointment twice daily and cetirizine 10 mg/day p.o. was initiated. Because skin lesions

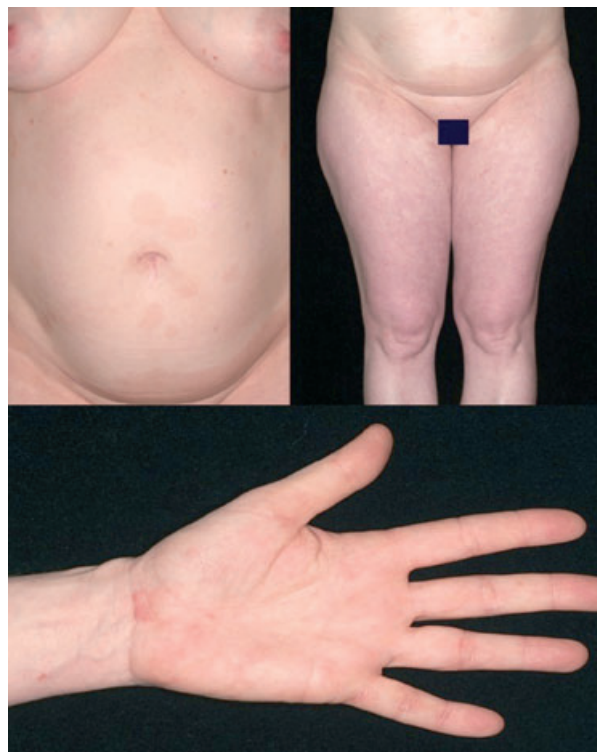


Figure 3. Post-inflammatory hyperpigmentation and slight erythema 8 weeks after initiation of immunoadsorption. At this time, prednisolone 7.5 mg/day was taken.

further spread and tense blisters appeared on the neck, back, abdomen, lower arms, legs and feet (Fig. 2), prednisolone was increased to 60 mg/day over the next 2 weeks and topical betamethasone 0.1% was changed to clobetasol propionate 0.05% ointment. Despite temporary improvement, skin lesions eventually progressed and the pruritus further aggravated leading to sleeping difficulties. Because the patient wanted to continue breast-feeding and further increasing the prednisolone dose was not advised by the consulted gynecologists, immunoadsorption (IA) was initiated (Therasorb-Ig Flex; Miltenyi, Bergisch-Gladbach, Germany). This IA device is based on a sepharose matrix coupled with polyclonal sheep antihuman Ig that specifically binds human IgG, IgA, IgM and IgE and can be reused for the same patient for up to 10 treatments. Ten IA were performed over 4 weeks in four cycles of two or three procedures on consecutive days (Fig. 1). IA was applied using peripheral venous access processing the twofold plasma volume in each procedure. Autoantibody levels could be reduced from 72,647 before IA was initiated to 199 U/mL after the 10th IA (Fig. 1). In parallel, skin lesions faded (Fig. 3), pruritus greatly improved allowing the stepwise reduction of prednisolone to 7.5 mg/day 5 weeks after the initiation of IA (Fig. 1). Eight weeks after initiation of adjuvant IA, all lesions had healed and prednisolone was omitted 4 weeks later. Over the following weeks, isolated vesiculae occurred followed by spontaneous remission. The patient continued breast-feeding throughout the whole treatment period and her son developed normally.

DISCUSSION

The pathogenic potential of anti-BP180 NC16A antibodies has been clearly demonstrated both *in vitro* and *in vivo*.^{15–18} BP180 NC16A-specific antibodies induced leukocyte-dependent dermal–epidermal separation in cryosections of human skin^{15,17} and subepidermal blistering accompanied by the immunopathological hallmarks of human bullous pemphigoid in neonatal mice.¹⁶ Because the pathogenic effect of PG sera has previously been abolished by preadsorption with synthetic peptides covering the N-terminal 24 amino acids of the BP180 NC16A domain, this portion seems to harbor the major pathogenic sites of autoantibodies in PG.¹⁹ The pathogenic importance of BP180 NC16A is underlined by the correlation of anti-BP180 NC16A autoantibody serum levels with the disease activity in patients with bullous pemphigoid.²⁰

For treatment of PG class II–IV, topical corticosteroids in combination with oral antihistamines frequently suffice. Adding low-dose oral prednisolone (0.25 mg/kg bodyweight per day) may occasionally be necessary to suppress lesion formation and the intense pruritus.²¹ Only rarely, like in our patient, higher doses of prednisolone are required which may be challenging when the patient, like in our case, is breast-feeding. Because placental antigens appear to trigger the autoimmune response in patients with PG, and maternal skin lesions and serum antibody levels usually fade within a few months after birth, removal of autoantibodies is a rational and particularly attractive therapeutic option in PG. Serum autoantibodies can be removed by plasmapheresis and IA. In contrast to plasmapheresis, IA specifically adsorbs Ig, does not require substitution with human albumin or fresh-frozen plasma, and allows processing of the double plasma volume. IA has been intensively used as adjuvant treatment in patients with severe and/or refractory pemphigus (reviewed in²²) and treatment recommendations for autoimmune bullous diseases with IA have been published by Germany, Austrian and Swiss experts in this field.²³

The strength of IA lies in the swift reduction of circulating antibodies which, like in our patient, is paralleled by a reduction of lesions. In our patient, the reduction of serum autoantibody levels was accompanied by serum total IgG levels that decreased just below the lower normal value of 7 g/L. Contraindications to IA treatment include known hypersensitivity towards IA materials or anticoagulants, extreme bleeding tendency and severe cardiovascular disease. When peripheral venous access is possible, IA is a safe procedure with only six adverse events in 50 patients with immunobullous disorders subjected to more than 500 IA procedures.²² The most frequently observed adverse reaction of IA in patients with immunobullous disease were *Staphylococcus aureus* sepsis in two patients with central venous access, venous thrombosis (in two patients), and citrate-induced reactions such as paresthesia and hypocalcaemia (in two patients).²²

So far, only two patients with PG have been reported to have received adjuvant IA. In both patients, rapid clinical remission could be achieved and serum autoantibody levels to BP180 decreased in parallel with the clinical response. Systemic corticosteroids were tapered and the disease could be controlled.^{24,25}

In conclusion, IA appears as a safe and effective adjuvant treatment option for severe PG. In PG, IA is particularly attractive

because, in contrast to the other immunobullous diseases, immune cells are usually silenced after the placenta is removed and the patients do not require long-term immunosuppression.

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