

Successful immunoapheresis of bullous autoimmune diseases: pemphigus vulgaris and pemphigoid gestationis

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Summary

Background: Immunoapheresis/immunoabsorption is a specific tool to remove immunoglobulins and immune complexes from the circulation. Immunoapheresis is successfully used in various autoantibody-mediated diseases (such as autoimmune renal disease and others). In dermatology immunoapheresis is increasingly applied as an adjuvant treatment for severe autoimmune bullous diseases.

Case report: We successfully employed adjuvant immunoapheresis to treat a 57-year-old man with life-threatening pemphigus vulgaris and a 30-year-old pregnant woman with severe pemphigoid gestationis. Immunoapheresis induced a rapid improvement and almost complete clearance of clinical symptoms without notable side effects. The clinical improvement was paralleled by a decline of the pathologic circulating autoantibodies. Following stabilization of his disease with immunoapheresis, the pemphigus vulgaris patient was continued on rituximab and remained almost free of symptoms for the next 12 months. The patient with pemphigoid gestationis was subsequently treated with systemic corticosteroids until the symptoms of her self-limited disease ceased.

Conclusion: Immunoapheresis might represent an excellent therapy for certain patients with severe pemphigus vulgaris or pemphigoid gestationis, unresponsive to conventional treatment regimens. We observed rapid improvement of clinical symptoms and no notable side effects.

Introduction

Pemphigus vulgaris (PV) is characterized by erosions affecting the skin and mucous membranes. Histopathological analysis reveals acantholysis which leads to suprabasal blistering. The pathophysiological cause is IgG autoantibodies against desmoglein-1 (Dsg-1) and desmoglein-3 (Dsg-3) [1]. Desmogleins belong to the family of desmosomal cadherins, glycosylated transmembranous proteins that are found in the desmosomes of epithelial cells. Desmosomal cadherins mediate intercellular adhesion of keratinocytes via homotypical and probably heterotypical protein formation. Binding of autoantibodies to specific extracellular domains of

Dsg-1 and Dsg-3 destroys their ability to form proteins. This in turn causes loss of adhesion between epithelial cells. Histological analysis shows acantholysis and later blistering. Patients with mucocutaneous pemphigus have autoantibodies against Dsg-1 as well as Dsg-3. The course and severity of disease are determined by the level of circulating pathogenic autoantibodies [2].

Pemphigoid gestationis (PG) is a rare skin disorder occurring during pregnancy (usually beginning in the 4th to 7th month) which resembles bullous pemphigoid (ca. 1 : 60 000 pregnancies) [3]. In such patients the autoantibodies usually target the structural proteins of

hemidesmosomes, the pemphigoid antigen 2 (BPAG2 = collagen type XVII), a 180 kD protein with collagen domains. Autoantibodies against the 230 kD bullous pemphigoid antigen 1 (BPAG1), which is located in the intracellular plaque of the hemidesmosome, are much rarer.

The autoantibodies are activated after binding complement. Chemotaxis causes migration of (eosinophilic) leukocytes into the basement membrane zone. These release lysosomal enzymes and proteinases such as elastase and gelatinase and destroy the antigen structure protein. This ultimately leads to blistering in the lamina lucida and subsequently to

junctional blistering. Pemphigus disorders are initially treated with corticosteroids which are usually administered together with various immunosuppressants (e.g., azathioprine, mycophenolate mofetil, intravenous immunoglobulins). Long-term therapy should be as corticosteroid-free as possible. PG is treated with topical and systemic corticosteroids, often in combination with antihistamines [4]. In rare instances, these conventional therapies are unable to control the disease. In such patients, immunoapheresis/immunoadsorption (IA) appears to be an excellent option. In the following, we report our own experience with therapy of a man diagnosed with PV a woman with PG. In both patients the disorder was successfully brought under control and progression was temporarily halted.

Patient 1

A 57-year-old man reported that painful erosions had appeared on the oral mucosa several weeks before he came to our clinic. The lesions spread over the entire skin with significant hair loss on the scalp and beard area (Figure 1a, b). The patient appeared to be in a dramatically worsened state of overall health and nourishment.

Clinical inspection revealed generalized, large, painful burning and oozing erosions with epidermal shreds around the margins. Some of the lesions were covered by serous-hemorrhagic crusts with areas of impetiginization. Intact, easily opened blisters were also found, especially on the extremities. Direct and indirect Nikolsky signs were positive on the entire skin. The mucous membranes on the glans and oropharynx were highly eroded.

Histological analysis of skin and mucous membranes showed typical separation and suprabasal blistering, acantholytic cells in the separation, and individual keratinocytes on the blister floor in a classic tombstone pattern.

Direct and indirect immunofluorescence studies (IF) showed reticulated IgG deposits on the keratinocyte cell membranes (titer 1 : 2 560).

ELISA (MBL, Nagoya/Japan) tests done at baseline showed anti-Dsg-1 autoantibody levels of 162.4 U/ml (normal values < 14 U/ml) and anti-Dsg-3 autoantibody levels of 149.9 U/ml (normal values < 7 U/ml). Circulating autoantibodies

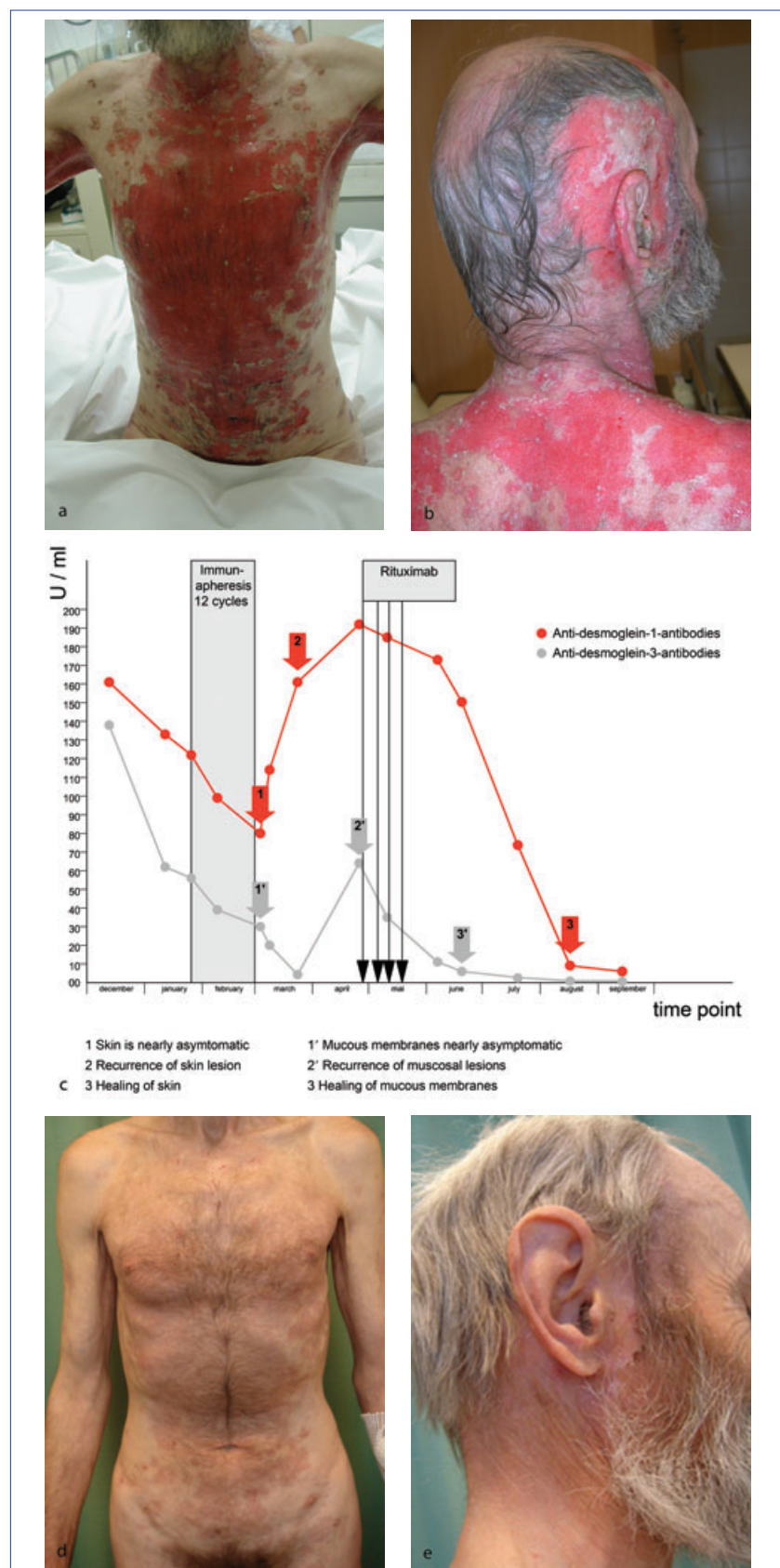


Figure 1: Involvement of the entire trunk by extensive confluent erosions; note crusts on the margin of erosions (a), involvement of hair follicles leads to extensive Pemphigus-alopecia (b). Changes of desmoglein-1 and desmoglein-3-autoantibody-levels under treatment with immunoadsorption and rituximab. Skin-lesions correlated well with the anti-dsg-1-antibody-levels, mucosal erosions with anti-dsg-3-antibody-levels (c). Complete remission with discrete postinflammatory hyperpigmentation (d) and hair-regrowth following therapy (e).

were measured regularly over the course of disease. This revealed a close correlation between the autoantibody levels and the severity of clinical disease (Figure 1c).

Therapy and outcome

Given the life-threatening nature of the illness, after PV was confirmed steroid-pulse therapy was promptly initiated with 1 g prednisolone i.v. per day [5]. At the diminished weight of the patient of 51 kg this corresponded to about 20 mg/kg. Azathioprine (2×50 mg orally per day) was given in combination. The steroid dose was continually reduced and on day 13 was switched to oral 120 mg 6-methylprednisolone. After initial improvement, there was worsening of the condition. Laboratory tests showing extremely abnormal liver values led to discontinuation of azathioprine after three weeks.

Oral steroids were then combined with intravenous immunoglobulin (2 g/kg for 4 days, 2 cycles in 3 week-intervals). Due to life-threatening skin and mucosal symptoms, repeated septicemia, and continued high autoantibody levels despite continuous oral steroid therapy (2 mg/kg body weight), we began a 6-week course of immunoapheresis therapy.

Immunoapheresis

Using a sepharose matrix with polyclonal anti-human sheep antibodies acting as a ligand (Ig-Therasorb®), 7 200 ml plasma per cycle was desorbed [6]. After the sixth IA session, reepithelialization was observed; after the twelfth and last session, the skin was nearly fully healed and the mucous membranes were completely healed (Time point 1.1' in Figure 1c). The serum levels of autoantibodies to Dsg-1 and Dsg-3 also decreased respectively. Four weeks after stopping IA skin lesions reappeared despite oral steroid therapy consisting of 10 mg 6-methylprednisolone/day; Dsg-1 autoantibody levels of 161.2 U/ml (Time point 2, Figure 1c) were measured. After another four weeks, anti-Dsg-3 autoantibody levels were 64.4 U/ml and mucosal erosions reappeared as well (Time point 2' in Figure 1c). We now initiated therapy with rituximab in a scheme similar to lymphoma therapy (375 mg/m^2 body surface area), initially combined with 10 mg 6-methylprednisolone a.d. (alternate day) which was gradually tapered over 12 weeks [7]. Within three months,

the symptoms resolved. The mucous membrane lesions healed 2 months earlier than the skin lesions. Anti-Dsg-3 levels were 6.0 U/ml (Time points 3' and 3 in Figures 1c, 1d, e). The patient remained in remission for the next 12 months.

Patient 2

A 30-year-old woman who was in week 32 of pregnancy reported that 3 days before she came to the clinic, she had developed extreme pruritus which was followed 48 hours later by a generalized rash. Clinical inspection showed a generalized, intensely pruritic, slightly elevated, partly urticarial erythema with areas with a multiforme appearance. The lesions were confluent on the abdomen and proximal extremities, forming large patches with taut vesicles on their margins and then later in the center as well (Figure 2a).

Histological analysis showed normal differentiation of the epidermis. Underneath there was extensive separation and blistering. Direct immunofluorescence revealed linear C3 deposition along the basement membrane zone. A complement binding test on human split-skin was positive.

Baseline ELISA (MBL, Nagoya/Japan) testing showed autoantibodies against the NC16A domains of BP180. Levels of 30.0 U/ml (normal values < 9.0 U/ml) were measured. Ten days later, levels had reached 51.0 U/ml. During the observation period, there was significant correlation between autoantibody levels and clinical appearances (Figure 2b).

Therapy and outcome

The patient complained mainly of excruciating pruritus. She was admitted to the hospital and therapy with topical steroids (diflucortolone valerate O/W emulsion 2 x/daily) was begun. This was applied generously to lesional skin. Systemic therapy was also initiated with 60 mg 6-methylprednisolone (Urbason®) at a body weight of 55 kg per day orally and 60 mg i.v. diphenhydramine hydrochloride (Dibondrin®) 2 x/day. Disease activity improved only moderately. After the patient developed new lesions and blisters, we decided to initiate IA as adjuvant therapy [8].

Immunoapheresis

A total of 15 IA (14 prenatal, 1 postnatal) sessions were performed using Therasorb®

with processing of 7 200 ml plasma per cycle. After 3 IA sessions in 5 days, the disease stopped progressing, and after two further sessions clinical symptoms disappeared (Figure 2c). The autoantibody level decreased parallel to IA after three sessions by 89 %, but then increased slightly to 41.2 % of baseline levels. Still, the clinical condition was able to be maintained with low-dose corticosteroids (10 mg/day) and with continued IA treatment (2-3 sessions weekly) and one IA each on the two last days before the planned Caesarean section.

Two days after the Caesarean section the patient relapsed. Increased autoantibody levels were also detected (Figure 2b). The steroid dose was increased to 60 mg/day and the patient resumed immunoapheresis. She refused further cycles due to complications related to caring for her baby. The steroid dose of 80 mg 6-methylprednisolone was steadily reduced and symptoms disappeared completely 14 days after birth, despite relative high autoantibody levels. Therapy was tapered over another 6 weeks at 4 mg 6-methylprednisolone.

Discussion

The pathophysiology of PV is mediated by anti-desmoglein autoantibodies against BPAG2, which triggers an inflammation cascade [9]. These autoantibodies are thus the rationale for the use of IA in severe and treatment-refractory disease. IA is used in such cases in place of plasmapheresis, which is much less specific. The plasma taken from the patient is processed by an immunoglobulin-binding matrix which selectively desorbs the immunoglobulins from the plasma. To avoid rebound, therapy is combined with systemic corticosteroids or also immunosuppressant drugs. A consensus report recommended that the induction phase consist of 3-4 treatments on consecutive days with high-affinity IgG-absorbers (e.g. Immunosorba®, Globaffin®, Therasorb®); subsequent therapy should be tailored to disease activity with regular clinical assessment of therapy success and measurement of disease-specific autoantibody levels [6]. Successful use of Therasorb® has been reported in paraneoplastic pemphigus, PV, and PG [10].

Our patients had very severe disease. After conventional therapy failed, disease activity was able to be stabilized by IA

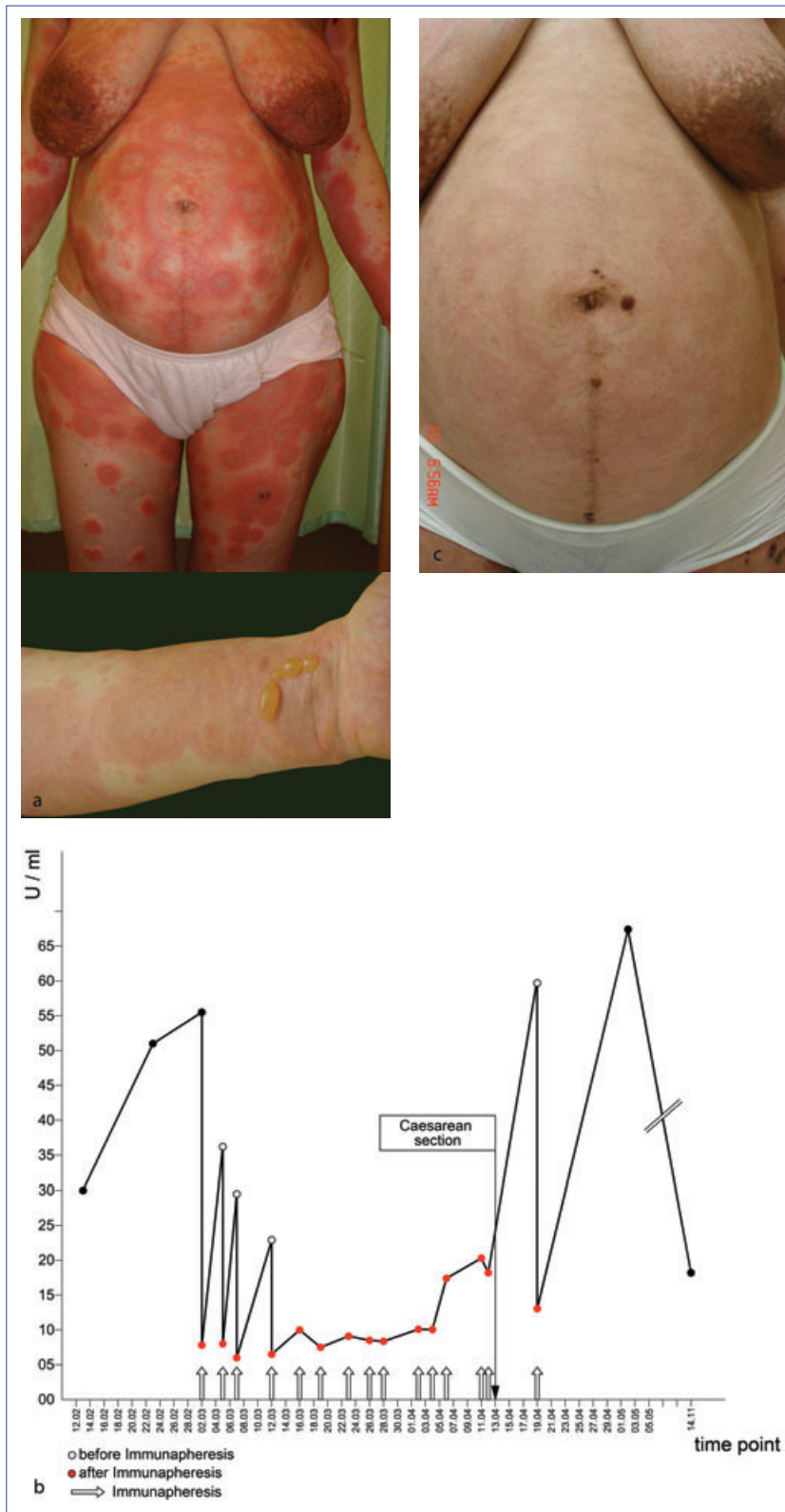


Figure 2: Generalised multiform- and urticaria-like eruptions and tense blisters within the lesions (a). Concentrations of circulating BPAG2 antibodies (b). Healing after the 5th immunoapheresis. Postinflammatory hyperpigmentation and crusts remain of the former lesions (c).

and progression was halted temporarily. To avoid rebound phenomena, IA was combined with systemic corticosteroids. Nevertheless, both patients experienced

a renewed increase in circulating autoantibodies and clinical recurrence following IA. The pemphigus patient was thus given rituximab, combined with low-

dose oral steroid therapy [11]. This brought about a dramatic reduction in pathogenetic autoantibody levels [12]. There were no apparent negative effects on total IgG.

PG is by nature a self-limiting disease. The post-partum relapse experienced by our patient was quickly brought under control with high-dose oral steroids. Steroid therapy was discontinued over the following 8 weeks, and the patient remained asymptomatic.

The potentially excessive autoantibody production observed suggests that while immunoapheresis can cause a rapid decrease in circulating autoantibodies and immune complexes, adjuvant therapy (conventional immunosuppression or rituximab) is needed to block later production of autoantibodies. The rising and falling serum levels of circulating autoantibodies during IA cycles suggests a redistribution of tissue-bound autoantibodies in the intravascular space (Figure 2b) [13]. Autoantibody overproduction, on the other hand, as observed in both patients after IA therapy, seems to be due to a reactive, excessive production following a decrease in autoantibody levels. The possibility cannot be ruled out, however, that this effect is simply due to increased disease activity. This hypothesis has been supported by a publication by Goldammer A. and colleagues who showed that there was a lacking increase free light chain synthesis and thus no feedback mechanism regulating immunoglobulin synthesis after IA [14]. This study included patients with various autoimmune disorders, although none had bullous skin disease. Zillikens and Schmidt reported that there was no increase in post-production of autoantibodies after IA was administered to pemphigus patients, but rather there was a continued suppressant effect [15]. This may be explained by variation in disease severity.

In summary, while IA is a time-consuming novel therapy, it can be useful in severe bullous skin disease, presenting an excellent option for bringing acute clinical symptoms under control. The use of IA is especially relevant in PG given that autoreactive B and T lymphocytes do not need to be addressed due to the self-limiting nature of the disease. Longer-term therapy and stabilization appear to only be possible in combination with traditional forms of therapy. <<<

Conflict of interest

None.

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