Case Report

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Adjuvant Treatment of Recalcitrant Bullous Pemphigoid with Immunoadsorption

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Key Words
Bullous pemphigoid · Immunoadsorption · Immunoapheresis

Abstract
Elimination of pathogenic autoantibodies by immunoadsorption (IA) has been described as an effective adjuvant treatment in severe bullous autoimmune diseases, especially in pemphigus. There is much less experience in the treatment of bullous pemphigoid (BP). BP was diagnosed in a 62-year-old Caucasian woman presenting a pruritic rash with multiple tense blisters. Standard treatments with topical and oral corticosteroids, steroid-sparing agents including dapsone, azathioprine, mycophenolate mofetil (MMF) and intravenous immunoglobulins were ineffective or had to be discontinued due to adverse events. An immediate clinical response could be achieved by two treatment cycles of adjuvant protein A immunoadsorption (PA-IA) in addition to continued treatment with MMF (2 g/day) and prednisolone (1 mg/kg/day). Tolerance was excellent. Clinical improvement remained stable after discontinuation of IA and went along with sustained reduction of circulating autoantibodies. Our data demonstrate that PA-IA might be a safe and effective adjuvant treatment in severe and recalcitrant BP.

Introduction

Bullous pemphigoid (BP) is a subepidermal bullous autoimmune disease. Autoantibodies are directed against the hemidesmosomes. The major target antigens are BP180 and BP230 [1]. BP commonly affects elderly people. Characteristic features are pruritic rash and tense blisters. Generally, BP can be effectively treated by topical or systemic corticosteroids either alone or in combination with dapsone or steroid-sparing immunosuppressive agents such as methotrexate, azathioprine or mycophenolate mofetil (MMF) [2]. In rare cases, stabilization cannot be achieved by these therapies.

The removal of circulating autoantibodies by immunoadsorption (IA) has been described as an effective adjuvant treatment in bullous autoimmune diseases, especially in severe pemphigus. In BP there is only limited experience with the use of IA.

Case Report

A 62-year-old Caucasian woman was admitted to our clinic with a 4-week history of a pruritic rash and progressive epidermal blistering. Combined treatment with oral methylprednisolone (0.6 mg/kg/day) and topical corticosteroids had already been initiated by her dermatologist, but new blisters continued to arise. The patient had a medical history of hypercholesterolemia, arterial hypertension, multiple sclerosis and depression. Her long-term medication included hydrochlorothiazide, acetylsalicylic acid, carbamazepine, tramadol and nitrendipine and had not been changed for several months.

Clinical examination revealed generalized erythematous urticarial plaques and tense blisters, erosions and crusts covering the breasts, back and extremities. The mucous membranes were unaffected. Histology of a skin biopsy showed a subepidermal blister and an eosinophilic infiltrate. Direct immunofluorescence microscopy of a perilesional skin biopsy revealed linear deposits of C3 at the dermoepidermal junction (fig. 1a). Circulating IgG autoantibodies binding to the epidermal side of the artificial blister in 1M NaCl-split human skin were detected by indirect immunofluorescence microscopy (fig. 1b). Enzyme-linked immunosorbent assay revealed high levels of anti-BP180 antibodies (MESACUP BP180®, MBL; 778 U/ml; positive >9 U/ml), but no anti-BP230 antibodies (Anti-BP230-CF-ELISA®, Euroimmun AG). These findings confirmed the diagnosis of BP.

Following exclusion of glucose-6-phosphate dehydrogenase deficiency, dapsone (1.5 mg/kg/day) was administered in

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combination with oral prednisolone (0.5 mg/kg/day) and topical betamethasone valerate 0.1% cream. Blister formation temporarily decreased, but after a period of partial remission, disease activity accelerated again. As a consequence, a high-dose intravenous steroid pulse was administered (100 mg dexamethasone on 3 consecutive days). The clinical course was complicated by a febrile cutaneous bacterial infection emerging from the site of an intravenous infusion line. Prednisolone was continued at a daily dose of 0.3 mg/kg. Following determination of thiopurine methyltransferase activity, azathioprine (1.3 mg/kg/day) was initiated while dapsone was continued. Due to drug-related myelotoxicity with recurrent lymphocytopenia and granulocytopenia, the dose of azathioprine could not be increased further and the clinical response remained insufficient. We subsequently added pulses of high-dose intravenous immunoglobulins (total dose 2 g/kg). 3 cycles were administered in 4-week intervals, but the clinical effect was poor. In the meantime, azathioprine was switched to MMF (1 g/day). However, MMF had to be discontinued due to recurring lymphocytopenia and granulocytopenia. Under the assumption of an additional myelotoxic drug effect, carbamazepine was tapered over 6 weeks and finally stopped before MMF was recommenced (2 g/day). Dapsone was discontinued. At this point, 4 months after our first diagnosis of BP, disease activity was invariably high with more than 50 blisters arising every day (fig. 2a, b). In addition, anti-BP180 antibodies increased dramatically (9,476 U/ml) and anti-BP230 antibodies were detectable for the first time (191 RU/ml, positive >20 RU/ml). A clinical breakthrough was achieved following initiation of adjuvant protein A immunoadsorption (PA-IA). Two cycles of IA treatment on 3 consecutive days were administered with an interception of 14 days. Plasma was separated by a cell separator device (Cobe Spectra®, Gambro). IA was performed using a pair of regenerable protein A Immunosorba® columns (Fresenius). While one column was loaded, the other was regenerated by an adsorption-elution device (ADAsorb®, Medicap). About 7 l of plasma was processed in each treatment, which took about 5 h. Within 48 h after the first treatment cycle, anti-BP180 antibodies decreased by 90% from 9,476 U/ml to 948 U/ml; anti-BP230 antibodies decreased from 191 RU/ml to 81 RU/ml (fig. 3). Significant clinical improvement was achieved within 24 h: blister formation ceased and lesions healed with residual formation of milia.

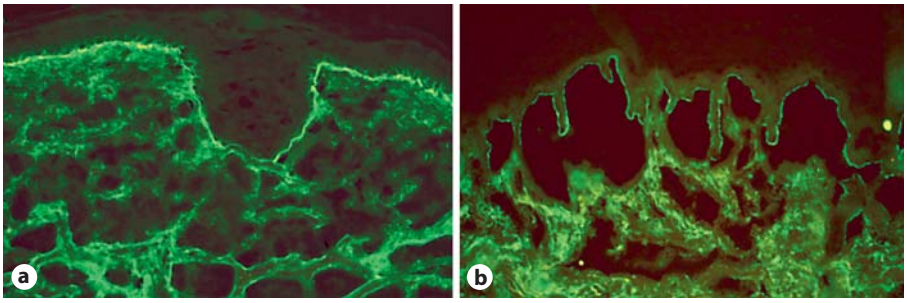

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Fig. 1. a Direct immunofluorescence microscopy of perilesional skin revealed linear deposits of C3 at the dermoepidermal junction. **b** Indirect immunofluorescence microscopy of human NaCl-split skin showed circulating IgG autoantibodies binding to the epidermal side of the artificial blister.

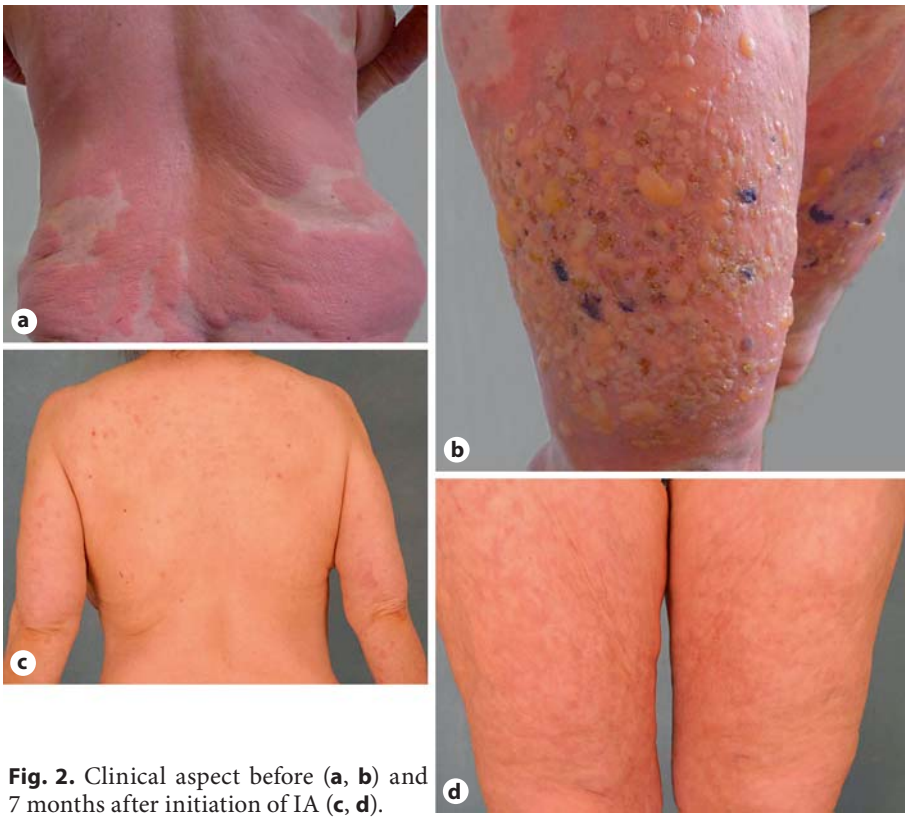

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Fig. 2. Clinical aspect before (**a**, **b**) and 7 months after initiation of IA (**c**, **d**).

Disease activity took a benign course and oral prednisolone (1 mg/kg/day) was gradually tapered. Seven months after PA-IA, immunosuppressive medication consisted of prednisolone (0.1 mg/kg/day) and MMF 2 g/day. The patient was almost free of skin lesions (fig. 2c, d) and the anti-BP180 antibody level decreased to 22.3 U/ml. One year after PA-IA, BP180 ELISA turned negative. Prednisolone was decreased to 0.03 mg/kg/day while MMF was continued.

Discussion

Extracorporeal treatments such as plasmapheresis and IA have been established to remove pathogenic antibodies in a number of autoimmune disorders, mostly in addition to pharmacologic immunosuppressive therapies. IA has recently been introduced as an adjuvant treatment in severe blistering autoimmune diseases [3]. According to a consensus meeting in 2005, adjuvant IA is a first-line therapeutic option to induce clinical remission in acute and severe pemphigus and epidermolysis bullosa acquisita. There is limited experience in the treatment of BP, but IA may be considered if the disease persists for longer than 3 months and is refractory to at least two adequate immunosuppressive therapies [4].

In contrast to plasmapheresis, IA selectively removes IgG. Substitution of plasma components (i.e. fresh frozen plasma, human albumin) is not required. A larger plasma volume can be processed in one session and fewer side effects occur [3–5].

IA is a two-step procedure. First plasma is separated from the cellular components by plasma filtration or centrifugation, and then immunoglobulins are removed by an adsorber. Commercially available adsorbers differ with regard to matrix (sepharose, cellulose and polyvinyl alcohol) and ligands (i.e. polyclonal anti-human sheep antibody, synthetic protein PGMA146, staphylococcal protein A, dextran sulfate, tryptophan and phenylalanine) [3, 5]. Reusable adsorbers containing either protein A, anti-human IgG sheep antibodies or the synthetic peptide PGAM146 can be reused several times in the same patient and show higher IgG depletion rates than single use adsorbers [4]. Interestingly, IA may also be used to treat IgA-mediated autoimmune diseases. Kasperkiewicz et al. [6] reported on the successful adjuvant treatment of recalcitrant linear IgA disease by IA using a tryptophan-based adsorber.

Experience in the use of IA in BP is limited. To our knowledge, only 4 cases have been reported so far [7, 8]. In 1997, Ino et al. [7] described the successful treatment of two patients suffering from severe BP with IA using a one-time dextran sulfate-conjugated cellulose column. In both patients a reduction of antibody levels as well as a significant clinical improvement was achieved, and immunosuppressive therapy could be tapered. No adverse events occurred.

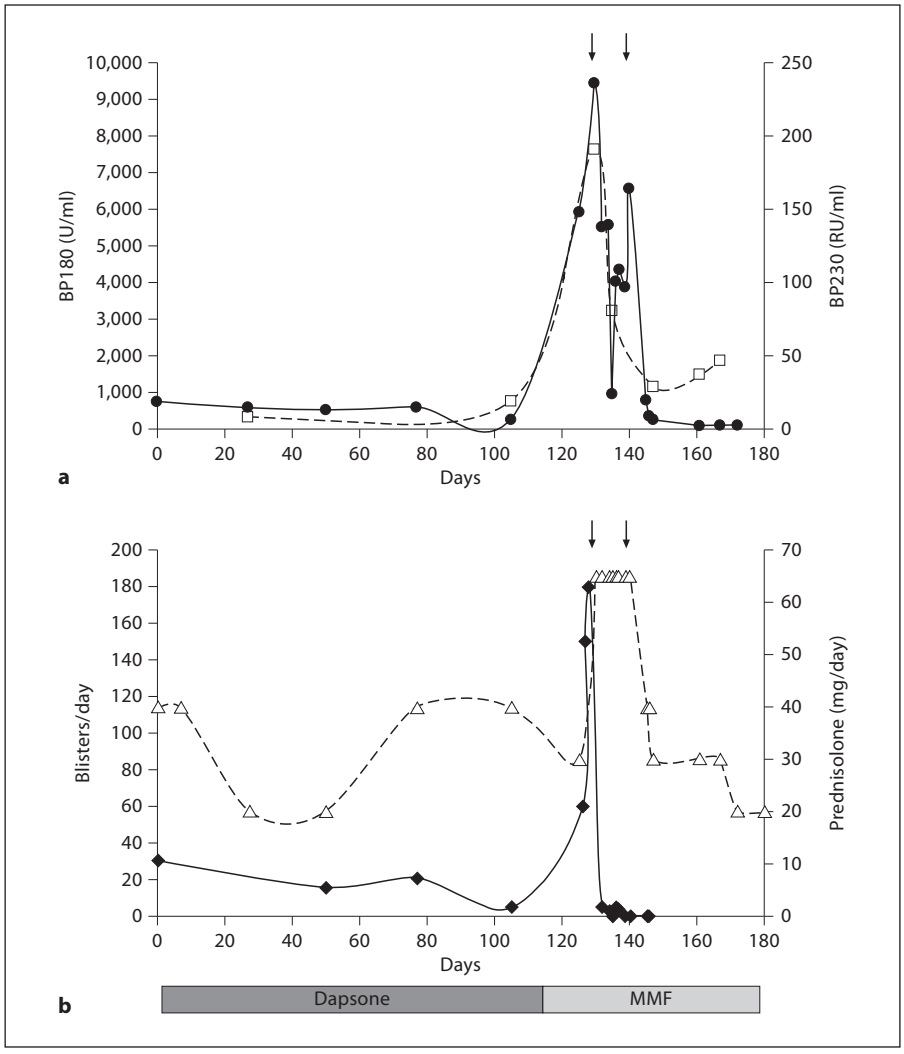

Fig. 3. a Autoantibody levels before and after IA. Black dots indicate the level of anti-BP180 antibodies (U/ml), white squares the level of anti-BP230 antibodies (RU/ml). **b** Blister count (black rhombi) and prednisolone dosage (white triangles) during the course of the disease. Adjuvant treatment consisted of dapsone and MMF. Each arrow indicates a cycle of three consecutive IAs.

In 2005, Herrero-González et al. [8] reported on two further patients who were successfully treated by one-time tryptophan adsorbers. Both patients showed a pronounced clinical improvement and a decline in antibody levels after therapy. No complications within 48 h after IA were observed. One patient, however, developed staphylococcal sepsis on the third day.

To our knowledge, we herein report the first case of BP treated with IA using reusable, semi-selective protein A columns (Immunosorba®, Fresenius). A decrease in autoantibody levels by up to 95% could be achieved by treatment with reusable IA systems in the setting of pemphigus [3]. We observed a 90% reduction in anti-BP180 antibodies 48 h after the first cycle of IA, followed by an increase within the next days (fig. 3). This phenomenon has been described previously and is most likely caused by redistribution of autoantibodies from tissue to the systemic circulation [3]. Repetitive IA on consecutive days is recommended to prevent this counterregulatory increase of autoantibodies [4]. More than one treatment cycle may be re-

quired and combination with immunosuppressive treatment is obligatory to maintain clinical remission. In case of repetitive IA, reusable systems should be preferred over one-time adsorbers for economic reasons. There are no controlled clinical trials comparing the effectiveness of the commercially available reusable adsorbers in autoimmune bullous diseases. In the setting of connective tissue diseases such as systemic lupus erythematosus, no significant differences were observed when comparing different systems with regard to clinical outcome [9, 10].

As in our patient, IA is generally well tolerated [4, 9, 10]. Anemia, orthostatic events, paresthesia and hypocalcemia are occasionally reported [4]. Severe adverse events such as bacterial infections and anaphylactic reactions are rare [3]. The substitution of immunoglobulins after IA does not effectively prevent therapy-associated infections and is therefore not recommended [11].

Our data support that IA is a safe and effective adjuvant treatment which may rapidly induce a clinical and serological response in severe and refractory BP, paving the way for standard immunosuppressive treatment to maintain remission. Controlled clinical studies are necessary to assess safety profiles and effectiveness in severe or refractory BP and to develop standardized treatment protocols with regard to adsorber systems, number of IAs and therapy intervals.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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