A Case of Bullous Pemphigoid Treated with Plasmapheresis and Pulse Cyclophosphamide

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A 54-year-old woman with severe bullous pemphigoid (BP) associated with insulin dependent diabetes mellitus (DM), who showed unresponsiveness to conventional therapy with corticosteroids in combination of either cyclosporine or dapsone, was successfully treated with plasmapheresis followed each time by 3 successive days of pulse therapy of cyclophosphamide (500mg, intravenously). After six times of plasmapheresis, anti-basement membrane zone (BMZ) antibody titer decreased from 1:1280 to 1:40 and no new lesions developed at all. In severe refractory BP patients with uncontrolled DM, plasmapheresis is one of the valuable treatment modalities for a short period and the need for corticosteroids thus avoiding corticosteroid induced side effects.

Herein we report a case of BP with uncontrolled DM who showed an excellent response to a low dose of corticosteroid and 150mg oral azathioprine following plasmapheresis and cyclophosphamide pulse therapy. (Ann Dermatol 5:(2) 146–150, 1993)

Key Words: Bullous pemphigoid, Cyclophosphamide, Plasmapheresis

Bullous pemphigoid (BP) is one of the chronic, generalized autoimmune bullous skin diseases in elderly persons. It is distinguished from pemphigus and is defined as a distinct entity clinically and histopathologically[1]. Clinically, BP is manifestated by tense and usually nongrouped bullae arising on a normal, erythematous or urticarial base. Direct immunofluorescence (DIF) shows linear deposition of IgG and C3 along the basement membrane zone (BMZ) in lesional and perilesional skin[2] by the presence of anti-BMZ antibodies in more than two thirds of patients with BP[1,3].

Corticosteoids have been the mainstay of treatment[4,5]. Over the years, the other agents, including a variety of immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, chlorambucil), sulfones, and sulfonamides, have been tried to reduce the side effects of longterm use of corticosteroids and to have the maximal effect in the treatment of BP[6-11]. But each agent produces its own range of problems, such as liver toxicity, bone marrow suppression, hemorrhagic cystitis and possible carcinogenic potential. In one recent review[4] conventional or adjunctive therapy which induced side effects were believed to be contributory to 50 percent of the deaths occuring in BP patients.

Recently, for reducing the risk of side effects resulting from the conventional therapy and for managing the patients recalcitrant to the conventional therapy, the plasmaheresis was introduced in the treatment of a variety of skin diseases[12].

Herin we report a severe BP patient with uncontrolled DM, who was resistant to conventional therapy, but showed significant clinical improvement after plasmapheresis and cyclophosphamide.

REPORT OF A CASE

A 54-year-old woman was admitted to the department of dermatology at St. Mary's Hospital with a four-month history of moderately pruritic erythematous patches and bullae. For four months,

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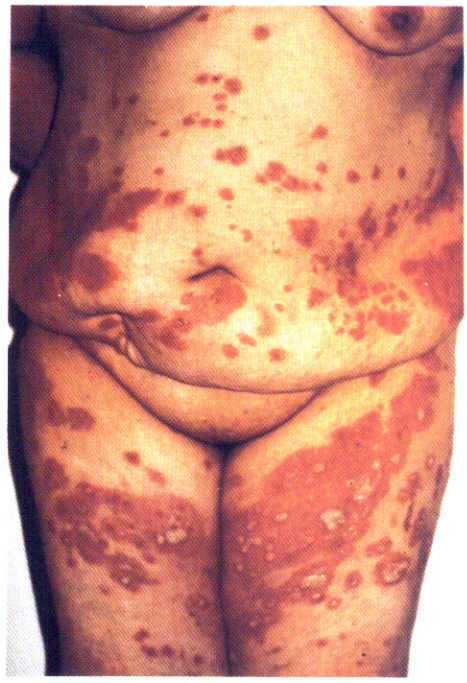

Fig. 1. Large tense bullae developed on the erythematous patch on the whole body before plasmapheresis.

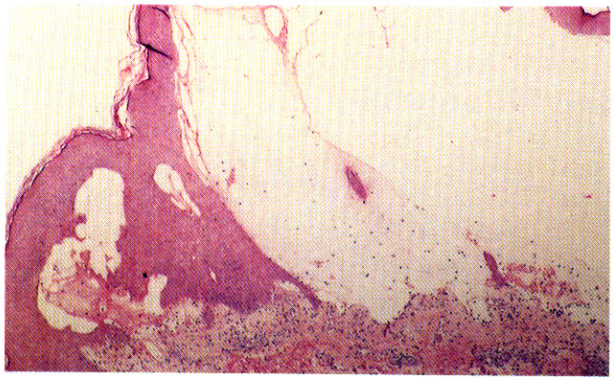

Fig. 2. A large subepidermal bulla contains a net of fibrin, eosinophils and neutrophils (H&E stain, ×40).

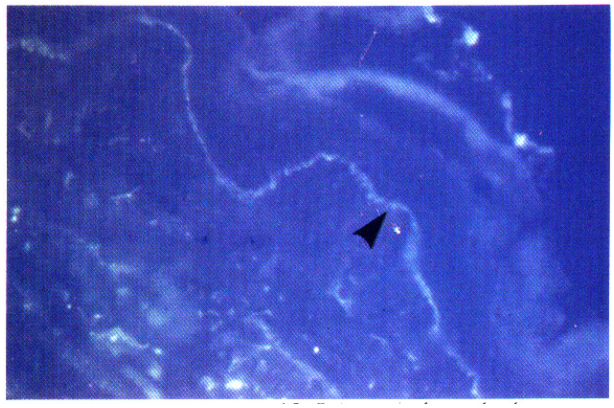

Fig. 3. Linear deposition of IgG (arrow) along the basement membrane zone (DIF, ×100).

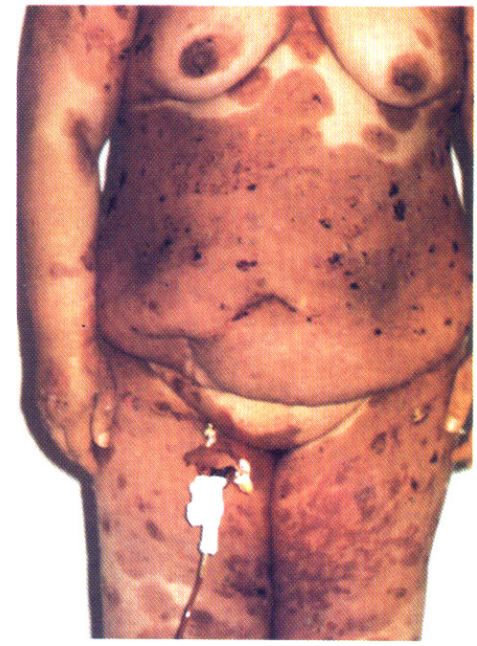

Fig. 4. After completion of three times plasmapheresis.

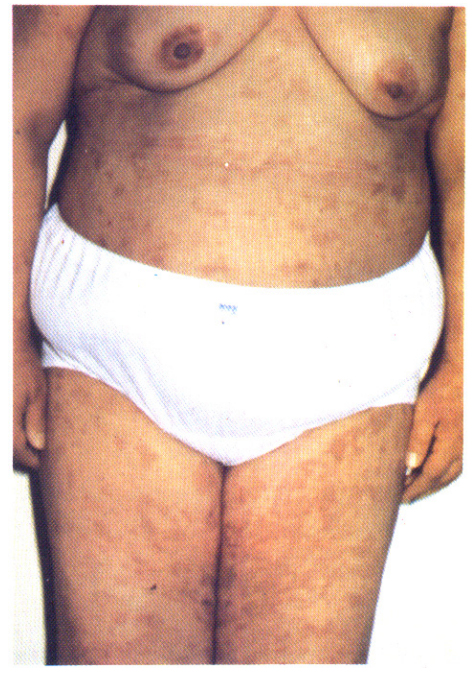

Fig. 6. After 6th plasmapheresis, erythematous plaques have almost completely resolved.

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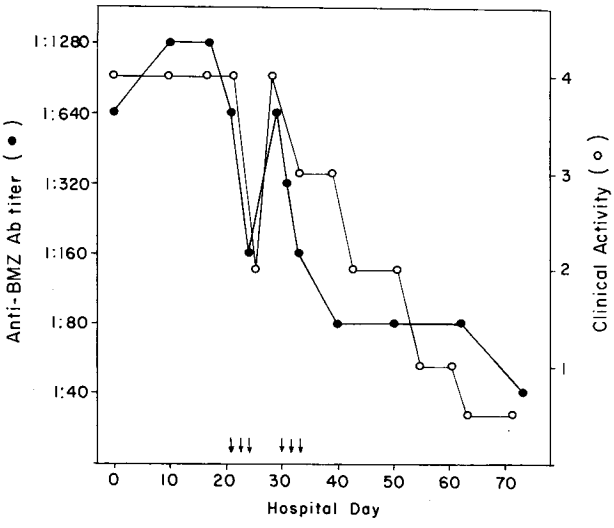

Fig. 5. Changes in titer of BP antibodies in serum and disease activity (based on blister formation activity) during plasmapheresis for bullous pemphigoid. Arrows indicate plasmapheresis.

she has been intermittently taking oral prednisolone (60mg/day) for the management of a pruritic blistering skin rash at local dermatologic clinic.

On admission, physical examination showed moderately pruritic, large tense, intact, and collapsed bullae on an erythematous base on the extensor surface of both arms, trunk, axilla, groin, anterior thigh and buccal mucosa (Fig. 1).

A biopsy specimen obtained from an early vesicle on the left thigh showed subepidermal a bulla with a normal epidermis. The underlying dermis showed scattered infiltrates of lymphocytes and some neutrophils as well as numerous eosinophils (Fig. 2). DIF studies of the biopsy specimen revealed a linear deposition of IgG and C3 at BMZ consistent with BP (Fig. 3). Indirect immunofluorescence (IIF) studies using foreskin as a substrate revealed anti-BMZ antibodies with a titer of 1:1280.

Abnormal laboratory studies included eop sinophil count 2871/mm^3 (15%), fasting blood sugar 193mg/dl, and urinary glucose level (3+). Other laboratory values including liver function test, renal function test, immunoglobulin, C3 & C4, serum protein electrophoresis, rheumatoid factor, ANA, ASO, anti-DNA, EKG, roentgenogram of chest and abdomen were within normal limits or negative.

Therapy was initiated with methylprednisolone succinate (120mg/day) intravenously and cyclophosphamide (100mg/day) orally. After two weeks of treatment, new bullae were still appearing on the trunk and hard palate. We added cyclosporine (400mg/day) orally for the replacement of cyclophosphamide but this additional therapy failed to have a beneficial effect. At this point, we could not continue administration of corticosteroid and immunosuppressive agents because of the corticosteroid related side effects, such as on aggravated diabetic condition, weight gain and hypertension. Despite insulin treatment and a diabetic diet, her fasting blood sugar level was not controlled.

After informed consent was given, the patient underwent plasmapheresis utilizing a discontinuous flow centrifugation system (KM® 8800, Kuraray, Japan). Fifty ml/kg of plasma were exchanged in each procedure. Immunoglobulin free 4% albumin solution was used as replacement solution. Pulse cyclophosphamide (500mg, intravenously) therapy was performed on day 3,4 and 5 immediately after plasmapheresis. The oral lesions as well as the skin lesions slowly resolved over the following week (Fig. 4). But on the 29th hospital day, anti-BMZ antibody titers increased to 1:1280 and new bullae were developed on the skin and oral cavity. On the 30th hospital day, we performed another consecutive plasmapheresis to aim at the removal of the residual redistributing anti-BMZ antibody, as previously. The schedule of treatment, and anti-BMZ antibody titers before and after plasmapheresis are shown in figure 5.

The patient's condition improved rapidly and the anti-BMZ antibody titer dropped to 1:80. Thereafter, we tapered off methylprednisolone and added oral azathioprine (150mg). Her body weight returned to normal and her blood sugar level decreased progressively. Ten months after discharge, the patient's serum anti-BMZ antibody titer is 1:40 and her conditions is still under good control with 5mg of oral prednisolone and 150mg of oral azathioprine (Fig. 6).

DISCUSSION

BP is an autoimmune disease in which circulating autoantibodies to a normal component of BMZ of stratified squamous epithelia are formed. Diagnosis is usually made on the basis of clinical features, the histologic characteristics of the subepidermal blister and immunologic criteria with deposition of IgG and/or C3 along the BMZ of epidermis on DIF[1,2]. Circulating BP antibody can be detected by IIF in the serum samples of 50% to 70% of patients[3].

BP is a disease of heterogenous nature. Some patients display a few localized lesions that tend to subside spontaneously, while others have a chronic course characterized by many lesions widely distributed over the cutaneous surface. As well as this clinical heterogeneity, the patient's underlying disease is the important factor in treatment response[13]. It is known that BP is easily controlled with moderate doses of corticosteroids[1,4,5], but infrequently, the addition of an immunosuppressant[4,5] is often proven to be effective when a moderate dose of corticosteroid therapy failed to control the development of new lesions[5-8]. The concomitant use of an immunosuppressant also permitted the rapid tapering of corticosteroid, thereby reducing the risk of untoward corticosteroid side effects, such as cushingoid features, hypertension or aggravation of existing diabetes mellitus[4,14]. For this reason, some authors insisted that an immunosuppressant without concomitant corticosteroid[14,15] should be preferentially considered in patients with insulin-dependent diabetes. In our cases, skin lesions had not improved despite the administration of a high dose of a corticosteroid and immunosuppressants (cyclosporine and cyclophosphamide) and DM was aggravated by corticosteroid therapy. Therefore, we could not continue conventional therapy for this patient.

Recently the use of plasmapheresis as an adjunctive to systemic corticosteroid therapy in the treatment of autoimmune disease patients unresponsive to the conventional therapy has been evaluated[16-19]. Plasmapheresis is to remove the noxious consituents out of the plasma of the patients and to replace it with a harmless substitute. Two methods of plasmapheresis are currently available; centrifugation (continuous and discontinuous flow) and filtration. The centrifugation method allows collection of white cells and platelets. In contrast, the filtration devices retain all cellular blood components. We applied discontinuous plasmapheresis, which is performed by removing blood from the patient and passing it through a discontinuous flow centrifuge to separate plamsa that contains auto-antibodies from celluar elements.

However, it has been known that an increase of antibody titer can be observed as a rebound effect ensuing from large or massive plasmapheresis and a transient clinical exacerbation might be induced in the plasmapheresis-treated BP[12,16]. In our patient, although clinical conditions and laboratory findings improved after the first plasmapheresis, the titer of anti-BMZ antibody returned to level before admission in 6 days later with development of new skin lesions. The reason for this antibody rebound phenomenon is assumed in part due to increased B-cell clones by means of a feedback cycle between circulating antibodies and their production[16]. To compensate for this phenomenon, Yamada et. al.[20] developed a modified method which represents a combination method that has the advantage of both centrifugation and filtration plasmapheresis in the treatment of BP. In their study, the removal of BP antibodies was performed selectively and effectively, therapy causing the titer of BP antibodies to gradually fall. The patient's clinical symptoms improved remarkably with the decrease in the titer of BP antibodies with no side effects.

To reduce the possibility of antibody rebound, the pulse cyclophospamide therapy subsequently following plasmapheresis was developed. It utilizes the increased vulnerability of pathogenic B cells to high dose cytotoxic drugs during the period of maximum antibody rebound induced shortly after antibody depletion[18]. In our case, the titer of anti-BMZ antibody on admission was 1:1280 and it decreased to 1:80 with six-time plasmapheresis and subsequent cyclophosphamide pulse therapy. Although we could not quantitify the rebound phenomenon of autoantibodies immediately following the first plasmapheresis, it seems that the down-regulation of antoantibodies might be the effect of cyclophosphamide pulse

therapy.

Plasmapheresis is generally well tolerated and safe. Major complications involve depletion of clotting factors, electrolyte imbalance, fluid overload that may lead to pulmonary edema, allergic reaction, including anaphylaxis to γ-globulin, infection, cardiac dysrhythmia and difficulty with vascular access[12]. But the risk in patients with BP who are receiving a high dose of corticosteroids and immunosuppressive drugs is not yet known well. In our case, although weight gain and decreased serum potassium level were developed during plasmapheresis, it was normalized soon after cessation of plasmapheresis. Previous reports suggested that there is no correlation between the IIF antibody titer and disease activity[5,21]. But our patient showed a consistent decrease of in the autoantibody tcter in parallel with clinical activity after plasmapheresis. The effect of plasmapheresis with pulse cyclophosphamide may have contributed to this discrepancy. After combined therapy of plasmapheresis with pulse cyclophosphamide, the patient's condition is still under good control with 5 mg of oral prednisolone and 150mg of oral azathioprine without side effects. Also DM is under good control by diet.

Our case informs us that plasmapheresis may have a role as an adjunctive therapy when conventional therapy is inadequate to control the disease owing to complications.

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