LETTERS TO THE EDITOR

Clearance Efficacy of Autoantibodies in Double Filtration Plasmapheresis for Pemphigus Foliaceus

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Plasma exchange is a therapeutic option in severe cases of pemphigus. Both centrifugal plasmapheresis and double filtration plasmapheresis (DFPP) are available, but the latter, newer, procedure currently prevails because of its safety advantage (1, 2). In DFPP, immunoglobulins (Igs) are selectively removed, while minimizing the loss of albumin (3). In several studies, the removal rates (RRs) of anti-desmoglein (Dsg) 1 and Dsg3 autoantibodies have been estimated by using serum antibody titres immediately before and after plasmapheresis (3). This simple estimation is designated RR1 in the present study. Given the data for anti-Dsg titres and Ig amounts in the exchanged effluents, however, we can calculate the corrected or compensated RR, named RR2 in this study, which reflects the elimination efficacy of antibodies more accurately than RR1. RR2 of pemphigus autoantibodies has been reported only in centrifugal plasmapheresis (4), but not in DFPP. This study examined RR2 of anti-Dsg1 autoantibody with reference to total immunoglobulins (Igs) in 4 cycles of DFPP performed in 2 patients with pemphigus foliaceus (PF).

PATIENTS AND METHODS

Two patients with PF were enrolled in this study.

Case 1. Case 1 was an 85-year-old Japanese man with erosions on his trunk and extremities. There was no involvement of the oral mucous membrane. He had had chronic myelomonocytic leukaemia for 6 months without treatment. Immediately before the start of DFPP, the enzyme-linked immunosorbent assay (ELISA) titres for Dsg1 and Dsg3 were 2,031 and <5 indices, respectively. Following administration of prednisolone (60 mg daily) and mizoribine (100 mg daily), DFPP was implemented twice in total on 2 consecutive days. Immediately after the second DFPP, anti-Dsg1 antibody was decreased dramatically to 220 index, with therapeutic success. However, the patient had severe sepsis, with serum IgG lowered from 1,320 to 407 mg/dl. Blood culture and culture of the tip of the central venous catheter was positive for *Staphylococcus aureus*. Serum albumin and fibrinogen levels were decreased from 3.5 to 2.5 g/dl, and 87 to >50 mg/dl, respectively. Over a period of 2 months after DFPP, prednisolone was tapered to 30 mg/day without clinical recurrence.

Case 2. Case 2 was a 48-year-old Japanese man who had had PF for 2 years, which was controlled with oral prednisolone (20–60 mg daily) plus cyclosporine (150 mg daily). However, flaccid vesicles and erosions continued to recur. Because of the adverse effects of corticosteroids (pulmonary embolism and avascular necrosis of the femoral bone), and of intravenous

high-dose Ig (thrombocytopaenia, platelet count <50,000 μl), 2 courses of DFPP were implemented on 2 consecutive days. The ELISA titre for anti-Dsg1 autoantibody was decreased from 88 to 18 and anti-Dsg3 antibody to <5, with therapeutic success. Serum albumin and fibrinogen levels were decreased from 4.0 to 3.7 g/dl, and 274 to 220 mg/dl, respectively. For 3 months after DFPP, no recurrence of symptoms was observed with prednisolone (20 mg/day) plus cyclosporine (150 mg daily).

For DFPP, an apheresis device (Plasauto iQ21) was used, with a primary membrane (Plasmaflo OP-05W) and secondary membrane (Cascadeflo EC-20W), all of which were from Asahi Kasei Kuraray Medical Co. Ltd, Tokyo, Japan. The serum levels of anti-Dsg1, anti-Dsg3, IgG, IgA, and IgM were monitored just before and immediately after each DFPP treatment. The exchanged effluents were also subjected to measurement of anti-Dsg1 antibodies and Igs. RR was calculated in two ways, as reported previously (4):

$RR1 = \{(Index[pre] - Index[post])\}/Index[pre] \times 100$ (%), where Index[pre] and Index[post] are the ELISA index values before and after a cycle of plasmapheresis, respectively.

$RR2 = \{Index[e] \times V[e]\}/\{Index[pre] \times V[body]\} \times 100$ (%), where $V[body] = V[plasma]/0.45$ (L), $V[plasma] = V[blood] \times (1 - hematocrit)$, and $V[blood] = weight [kg]/13$.

Note that Index[e] and V[e] are the ELISA index value and the volume of effluent, respectively, and V[body] is the total volume of body fluid containing autoantibodies and Igs.
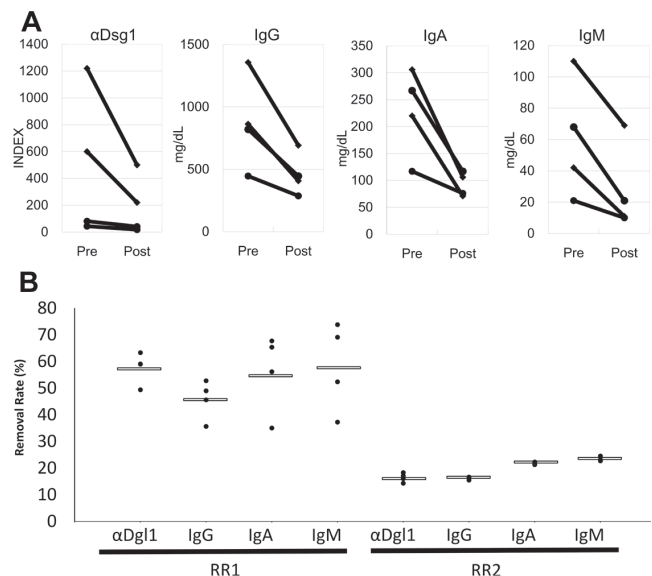

Fig. 1. Serum levels of anti-desmoglein (Dsg) 1 antibody and each class of immunoglobulins, and their removal rates by double filtration plasmapheresis (DFPP). (A) Serum levels of Dsg1 antibody, immunoglobulin (Ig)G, IgA and IgM were measured before (Pre) and after (Post) each cycle of plasmapheresis. (B) Removal rates (RRs) of anti-Dsg1 antibody, IgG, IgA and IgM. αDsg1: anti-Dsg1 antibody. Open bars indicate mean removal rates.

V[plasma] and V[blood] are the volumes of plasma and blood, respectively. V[body] was estimated from V[plasma], based on the fact that approximately 45% of the total body pool of Igs resides in the intravascular space (4). V[blood] was calculated based on the fact that 7.7% of body weight is approximately equal to V[blood].

RESULTS

All serum levels of anti-Dsg1 antibody and Igs were decreased after DFPP (Fig. 1A). RR1, representing the percentage of Igs eliminated from sera, and RR2, representing the corrected value of RR in consideration of the amount of removed autoantibodies in the effluents, were calculated. In the 4 cycles of DFPP, the mean values of RR1 and RR2 of anti-Dsg1 antibody were 57.7% and 16.4%, respectively (Fig. 1B). The RR2 of IgG tended to be lower than that of IgA or IgM, suggesting that IgA and IgM were eliminated more efficiently than IgG. The removal of anti-Dsg1 antibody was comparable to that of IgG. The total volume of plasma desorbed by each treatment was 0.51 and 0.55 l in Case 1 and 0.81 and 0.83 l in Case 2, respectively.

DISCUSSION

The merits of DFPP, including avoidance of albumin loss, and no need for fresh frozen plasma, have encouraged us to choose DFPP over centrifugal plasmapheresis. However, the clearance efficacy of DFPP has not been evaluated in a comparison with centrifugal plasmapheresis. Our study demonstrated that the mean values of RR1 (57.7%) and RR2 (16.4%) of anti-Dsg1 antibody are comparable to the reported values of centrifugal plasmapheresis (RR1, 48.4%; RR2, 16.4%) (4), although the number of patients is limited ($n = 2$). By RR2 analysis, we also found that IgM and IgA, pentamer and dimer Igs, respectively, are eliminated to a greater degree than IgG. As anti-Dsg1 antibody belongs to IgG

class, the autoantibody was removed at a similar rate to that of IgG.

Our results also highlight the need to avoid infection after DFPP. Patients with IgG levels < 100 mg/dl or IgM levels < 20 mg/dl for prolonged periods have an increased risk of recurrent and occasional life-threatening infectious episodes (5). Some reports suggest that transient depletions of IgG and/or IgM by plasmapheresis or immunosuppressive drug are not generally associated with an increased risk of infection. However, when DFPP is combined with long-term use of immunosuppressants and prednisolone and underlying leukaemia, DFPP could be the cause of sepsis, as observed in Case 1. While DFPP is effective for autoantibody removal, it should be stressed that IgM, IgA and IgG are eliminated in parallel with, or more profoundly than, autoantibodies.

The authors declare no conflicts of interest.

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