Case Letter

Plasmapheresis in Refractory Pemphigus Vulgaris: Revisiting an Old Treatment Modality Used in Synchrony With Pulse Cyclophosphamide

To the Editor:

Pemphigus vulgaris is an uncommon autoimmune blistering dermatosis characterized by painful mucocutaneous erosions. It can be a life-threatening condition if left untreated. The autoimmune process is mediated by autoantibodies against the keratinocyte surface antigens desmoglein 1 and 3.[1] Therapy is directed at lowering autoantibody levels with systemic corticosteroids and immunosuppressive agents. Use of these agents often is limited by collateral adverse effects.[2] Refractory disease may occur despite the use of high-dose corticosteroids or a combination of other immunosuppressants. The level of these pathogenic autoantibodies generally parallels the extent of disease activity, and removing them with plasmapheresis followed by immunosuppression should result in therapeutic response.[3] We report a case of refractory pemphigus vulgaris that was controlled with plasmapheresis used in synchrony with pulse cyclophosphamide.

A 48-year-old Chinese man first presented with mucocutaneous erosions 2 years ago, and a diagnosis of pemphigus vulgaris was confirmed based on typical histologic and immunofluorescence features. Histologic features included suprabasal acantholysis with an intraepidermal blister as well as basal keratinocytes attached to the dermal papillae and present along the entire dermoepidermal junction (Figure 1). Direct immunofluorescence demonstrated intercellular deposits of IgG and complements in the lower epidermis, and indirect immunofluorescence showed the presence of the pathogenic pemphigus autoantibodies. The patient was initially treated with prednisolone (up to 1 mg/kg daily) and mycophenolate mofetil (1 g twice daily) for 6 months with moderate disease response. Two months later he experienced a disease flare that was triggered by sun exposure and concomitant herpes simplex virus infection. He achieved moderate disease control with acyclovir, 3 days of intravenous immunoglobulin, and combination prednisolone and azathioprine. There was no other relevant medical history. For the last year, the patient received continuous prednisolone (varying doses 0.5–1 mg/kg daily), concomitant azathioprine (up to 3 mg/kg daily), and long-term prophylactic acyclovir, but he continued to have residual crusted erosions over the scalp and face (best score of 25 points based on the autoimmune bullous skin disorder intensity score [ABSIS] ranging from 0–150 points[4]). He was admitted at the current presentation with another, more severe disease flare with extensive painful erosions over the trunk, arms, legs, face, and scalp (80% body surface area involvement and ABSIS score of 120 points)(Figure 2)[4] that

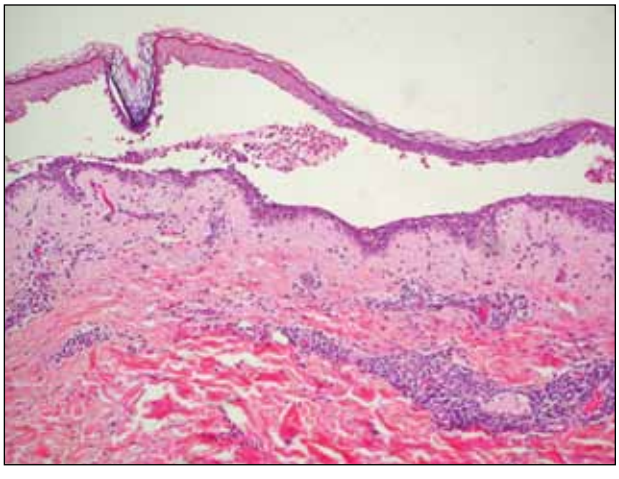

Figure 1. Histologic features of pemphigus vulgaris including suprabasal acantholysis with an intraepidermal blister as well as basal keratinocytes attached to the dermal papillae and present along the entire dermoepidermal junction (H&E, original magnification ×40).

Dr. Tay is from the Department of Dermatology, Changi General Hospital, Singapore. Drs. Linn, Pang, and Thirumoorthy are from Singapore General Hospital. Dr. Linn is from the Department of Hematology, and Drs. Pang and Thirumoorthy are from the Department of Dermatology.

The authors report no conflict of interest.

Correspondence: Liang Kiat Tay, MB ChB, MRCP, Changi General Hospital, 2 Simei St 3, Singapore 529889 (drtaylk@yahoo.com.sg).

occurred after azathioprine was temporarily ceased for 1 week due to transaminitis, and despite a temporary increment in prednisolone dose. There was, however, no significant oral mucosal involvement. The desmoglein 1 and 3 antibody levels were elevated at more than 300 U/mL and 186 U/mL, respectively (>20 U/mL indicates positivity). A 3-day course of pulse intravenous methylprednisolone (10 mg/kg) failed to achieve clinical improvement or reduction of antibody titers. The use of various immunosuppressive agents was limited by persistent transaminitis and transient leukopenia.

Because of remarkable morbidity, the patient underwent interim plasmapheresis for rapid disease control. Plasmapheresis was carried out through a pheresible central venous catheter. One plasma volume exchange was done each session, which was 5 L for the patient's body weight and hematocrit. Equal volume of colloid comprising 2.5 L of fresh frozen plasma and 2.5 L of 5% albumin was used for replacement. Plasma exchange was performed with a cell separator by discontinuous flow centrifugation with 4% acid citrate dextrose as an anticoagulant. For each session of plasmapheresis, 16 cycles of exchange (each processing approximately 300 mL of blood) was carried out, the entire process lasting for 4 hours. The coagulation and biochemical profile was checked after each session of plasmapheresis and corrected when necessary. The patient underwent 9 sessions of plasmapheresis over a 3-week period, synchronized with pulse intravenous cyclophosphamide (15 mg/kg) immediately after completion of the plasmapheresis sessions, resulting in a remarkable decrease in pathogenic antibody titers to near undetectable levels and clinical improvement (Figure 3). The extensive erosions gradually healed with good reepithelialization, and there was a notable reduction in the ABSIS score to 12 points. He received 3 more monthly treatments with pulse intravenous cyclophosphamide (15 mg/kg) and is currently maintained on oral cyclophosphamide (2 mg/kg daily) and low-dose prednisolone (0.3 mg/kg daily). There was no subsequent disease relapse at 6-month follow-up, with the ABSIS score maintained at 5 points, and no increase in pathogenic autoantibody titers. The patient subsequently was lost to follow-up.

Patients with severe disease or refractory cases of pemphigus vulgaris that have been maintained on unacceptably high doses of corticosteroids or immunosuppressants that cannot be tapered without a disease flare may develop remarkable adverse effects, both from medications and from long-term immunosuppression.[2] Our case illustrates the short-term benefit of plasmapheresis combined with immunosuppressants resulting in rapid disease control.

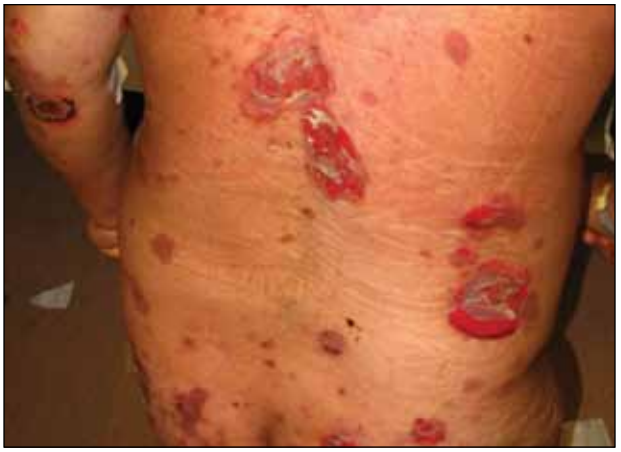

Figure 2. Acute flare of pemphigus vulgaris with extensive erosions of the trunk and arms (80% body surface area involvement).

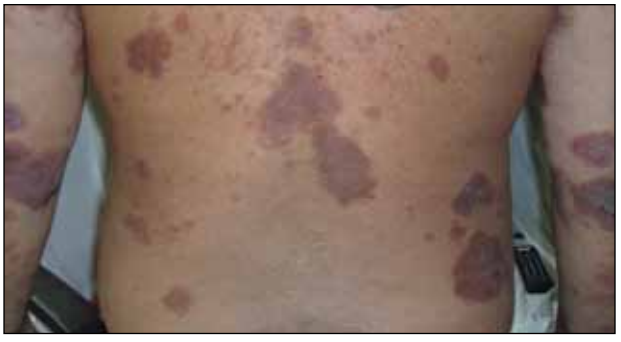

Figure 3. Clinical improvement of pemphigus vulgaris after 9 sessions of plasmapheresis synchronized with pulse intravenous cyclophosphamide over a 3-week period. The erosions were almost completely reepithelialized.

Plasmapheresis involves the selective removal of pathogenic materials from the circulation to achieve therapeutic effect, followed by appropriate replacement fluids. Treating pemphigus vulgaris with plasmapheresis was introduced in 1978 based on the rationale of removing pathogenic autoantibodies from the circulation.[3,5] Using desmoglein enzyme-linked immunosorbent assay, it has been shown that one centrifugal plasmapheresis procedure eliminates approximately 15% of the IgG autoantibodies from the whole body.[6] An average of 5 plasmapheresis sessions on alternate days usually is required to deplete the levels of pathogenic autoantibodies to near undetectable levels.[7] Our case required 9 plasmapheresis sessions over 3 weeks to achieve good therapeutic response.

It seems that using plasmapheresis to treat pemphigus vulgaris has fallen out of favor due to its inability to prevent the antibody rebound occurring during weeks 1 and 2 posttreatment. Because of a feedback mechanism, a massive antibody depletion by plasmapheresis triggers a rebound synthesis of more autoantibodies by pathogenic B cells to titers comparable to or higher than those before plasmapheresis.[8] The use of plasmapheresis should be supported by immunosuppressive therapy to prevent antibody feedback rebound. Due to the advent of available immunosuppressive agents in recent years, there is a resurgence in the successful use of this old treatment modality combined with immunosuppressive therapy in managing refractory pemphigus vulgaris.[7,8] At present there is no clear data to support the use of one immunosuppressant versus another, but our case supports the use of pulse intravenous cyclophosphamide, as documented in other reports.[7,9] The success of immunosuppressive agents at reducing antibody levels depends on the timing (immediately after plasmapheresis) as well as individual responsiveness to the immunosuppressant.[7]

Our armamentarium of therapies for refractory pemphigus vulgaris continues to evolve. A more selective method of removing antibodies by extracorporeal immunoadsorption has the benefit of higher removal rates and reduced inadvertent loss of other plasma components.[10] The combination of protein A immunoadsorption with rituximab, a monoclonal anti-CD20 antibody that induces B-cell depletion, also has been shown to induce rapid and durable remission in refractory cases.[11]

Our case shows that plasmapheresis can be a useful alternative or adjunctive intervention in pemphigus vulgaris that is not responding to conventional therapy or in cases when steroids or immunosuppressants are contraindicated. There is a definite role for such therapeutic plasma exchanges in the rapid control of potentially life-threatening disease. Its benefits are optimized when used in synchrony with immunosuppressants immediately following plasmapheresis to prevent rebound effect of antibody depletion.

Liang Kiat Tay, MB ChB, MRCP
Yeh Ching Linn, MBBS, MRCP
Shiu Ming Pang, MBBS, FRCP
Thamotharampillai Thirumoorthy, MBBS, FRCP

REFERENCES

1. Udey MC, Stanley JR. Pemphigus–disease of antidesmosomal autoimmunity. *JAMA*. 1999;282:572-576.
2. Huilgol SC, Black MM. Management of the immunobullous disorders. II. pemphigus. *Clin Exp Dermatol*. 1995;20:283-293.
3. Cotterill JA, Barker DJ, Millard LG. Plasma exchange in the treatment of pemphigus vulgaris. *Br J Dermatol*. 1978;98:243.
4. Pfutze M, Niedermeier A, Hertl M, et al. Introducing a novel Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) in pemphigus [published online ahead of print February 27, 2007]. *Eur J Dermatol*. 2007;17:4-11.
5. Ruocco V, Rossi A, Argenziano G, et al. Pathogenicity of the intercellular antibodies of pemphigus their periodic removal from the circulation by plasmapheresis. *Br J Dermatol*. 1978;98:237-241.
6. Nagasaka T, Fujii Y, Ishida A, et al. Evaluating efficacy of plasmapheresis for patients with pemphigus using desmoglein enzyme-linked immunosorbent assay [published online ahead of print January 30, 2008]. *Br J Dermatol*. 2008;158:685-690.
7. Turner MS, Sutton D, Sauder DN. The use of plasmapheresis and immunosuppression in the treatment of pemphigus vulgaris. *J Am Acad Dermatol*. 2000;43:1058-1064.
8. Roujeau JC, Andre C, Joneau Fabre M, et al. Plasma exchange in pemphigus. uncontrolled study of ten patients. *Arch Dermatol*. 1983;119:215-221.
9. Euler HH, Löffler H, Christophers E. Synchronization of plasmapheresis and pulse cyclophosphamide therapy in pemphigus vulgaris. *Arch Dermatol*. 1987;123:1205-1210.
10. Lüftl M, Stauber A, Mainka A, et al. Successful removal of pathogenic autoantibodies in pemphigus by immunoadsorption with a tryptophan-linked polyvinylalcohol adsorber. *Br J Dermatol*. 2003;149:598-605.
11. Shimanovich I, Nitschke M, Rose C, et al. Treatment of severe pemphigus with protein A immunoadsorption, rituximab and intravenous immunoglobulins. *Br J Dermatol*. 2008;158:382-388.