INTERNAL MEDICINE

□ CASE REPORT □

The Effects of Plasma Exchange on Severe Vasculitis with Diffuse Alveolar Hemorrhage

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Abstract

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis is a life-threatening disease characterized by rapidly progressive glomerulonephritis (RPGN) and diffuse alveolar hemorrhage (DAH). Glucocorticoids and immunosuppressants are commonly used to treat this disease but may induce irreversible side effects, particularly in elderly patients. We herein report the case of a 76-year-old woman with RPGN. After methylprednisolone pulse therapy, DAH occurred, and she required ventilatory support. After plasma exchange, her serum creatinine level improved, and she was discharged with home oxygen therapy. Immunosuppressive agents other than glucocorticoids were not required. In conclusion, plasma exchange with glucocorticoid therapy may be effective in treating severe ANCA-associated vasculitis in elderly patients.

Key words: antineutrophil cytoplasmic autoantibody-associated vasculitis, antineutrophil cytoplasmic autoantibody, diffuse alveolar hemorrhage, plasma exchange, rapidly progressive glomerulonephritis

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Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is a systemic vasculitis that predominantly affects the elderly (1, 2). For the primary induction of remission, AAV is generally treated with glucocorticoids, cyclophosphamide, or rituximab, a newly available therapy (3, 4). As initial therapy, the Japanese Society of Nephrology also recommends daily treatment with oral cyclophosphamide (25-100 mg/day) or intravenous pulses of cyclophosphamide (250-750 mg/m^2) with corticosteroids (5). Initial therapy with corticosteroids alone is indicated for cases in which aggressive treatment is required; however, the use of immunosuppressive agents is not desirable, particularly in patients older than 70 years.

Diffuse alveolar hemorrhage (DAH) is well known as a serious AAV symptom associated with high mortality (6, 7). In a study of 107 patients with biopsy-proven ANCA-associated microscopic polyangiitis and glomerulonephritis, the relative risk of death was 8.65 times higher in patients with pulmonary hemorrhage than in those without (7). However, the adverse effects of this therapy cannot be overlooked, and glucocorticoids and immunosuppressive agents may increase the susceptibility to infection, which is a strong indicator of mortality in patients with AAV (8).

Plasma exchange is a promising option for the treatment of AAV and is recommended in the guidelines (3, 5, 9). Because ANCA causes necrotizing glomerulonephritis and small vessel vasculitis, the removal of ANCA may contribute to the control of disease activity and the prevention of organ damage. Although the guidelines recommend the addition of plasma exchange to corticosteroid and cyclophosphamide therapy in patients with advanced kidney dysfunction, whether or not plasma exchange is effective in patients with alveolar hemorrhage is unclear (10).

We herein present the case of a 76-year-old woman with severe AAV and DAH who successfully achieved remission following prompt initiation of plasma exchange and low-dose prednisolone.

Case Report

A 76-year-old woman was admitted to our hospital with

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Table. Laboratory Findings on Admission.

Complete Blood Count		APTT (second)	26.8
White blood cell (μL)	8,800	PT (%)	75.6
Neutrophil (%)	69.2	Fibrinogen (mg/dL)	458
Eosinophil (%)	3.6	Antinuclear antibody (dilution)	40
Monocyte (%)	3.8	C3 complement (mg/dL)	98
Basophil (%)	0.4	C4 complement (mg/dL)	13.9
Lymphocyte (%)	23.0	PR3-ANCA (U/mL)	0.5
Hemoglobin (g/dL)	8.7	MPO-ANCA (U/mL)	336.0
Hematocrit (%)	28.8	Anti-GBM antibody	(–)
MCV (fL)	95	IgG (mg/dL)	2,175
MCH (pg)	28.6	IgA (mg/dL)	317
MCHC (%)	30.2	IgM (mg/dL)	83
Platelet (10^4/μL)	31	**Arterial Blood Gas (O_2 3L/min)**	
Serum Chemistry		pH	7.425
Urea nitrogen (mg/dL)	30.2	pO_2 (mmHg)	104.0
Creatinine (mg/dL)	2.35	pCO_2 (mmHg)	34.8
eGFR (mL/min/1.73 m^2)	16.2	HCO_3^- (mEq/L)	22.4
Sodium (mEq/L)	137	Base excess (mEq/L)	10.6
Potassium (mEq/L)	4.5	Anion Gap (mEq/L)	7.5
Chloride (mEq/L)	104	**Urinalysis**	
Calcium (mg/dL)	8.7	Gravity	1.009
Phosphorus (mg/dL)	4.5	pH	5.5
C-reactive protein (mg/dL)	5.84	Proteinuria	2+
Fe (μg/dL)	24	UPCR (g/gCr)	1.55
TIBC (μg/dL)	210	Hematuria	3+
Ferritin (ng/mL)	454	Red blood cell (/HPF)	10–19
		White blood cell (/HPF)	10–19
		Granular cast	2+

MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, eGFR: estimated glomerular filtration rate, TIBC: total iron binding capacity, APTT: activated partial thromboplastin time, PT: prothrombin time, PR3: proteinase-3, MPO: myeloperoxidase, ANCA: antineutrophil cytoplasmic autoantibody, GBM: glomerular basement membrane, RBC: red blood cell, UPCR: urinary protein to creatinine ratio

shortness of breath. One year before admission, she had presented with a three-month history of dry cough and was admitted to a local hospital for an examination. Chest-X ray showed ground glass opacity, and respiratory function testing showed an obstructive pattern. Macrophages were observed in the bronchoalveolar lavage fluid. She was diagnosed with idiopathic pulmonary fibrosis and discharged with home oxygen therapy only when she experienced shortness of breath. At the time, her serum creatinine level was 0.56 mg/dL, and there were no abnormalities on urinalysis. Three months before admission, she was again admitted to the local hospital for shortness of breath, anorexia, and weight loss (15 kg over 3 months), and her serum creatinine level was elevated to 2.23 mg/dL. In addition, urinary protein, hematuria (20-29 per high-power field), and markedly elevated myeloperoxidase (MPO)-ANCA were detected.

She was transferred to our hospital for further examination and treatment of suspected MPO-ANCA-associated glomerulonephritis. On admission, a physical examination revealed fine crackles, pale conjunctivae, clubbed fingers, body weight of 62.0 kg, body temperature of 36.7℃, blood pressure of 132/60 mmHg, pulse rate of 80 beats/min, percutaneous oxygen saturation of <90% on atmospheric air with a respiratory rate of 12-16 breath/min, and her Birmingham Vasculitis Activity Score was 24. As shown in Table, the serum creatinine level was 2.35 mg/dL, and the MPO-ANCA titer was 336 U/mL (normal range, 0-3.5 U/mL); normocytic anemia was detected.

On the day following admission, percutaneous renal biopsy was performed (Fig. 1). The histopathological findings revealed cellular crescents in 5 out of 10 glomeruli. No glomeruli showed mesangial proliferation or basement membrane changes. Tubulitis was found in the interstitial tissue and fibrinoid necrosis in the interlobular artery. Immunofluorescence studies did not reveal deposits in the glomeruli. These findings were compatible with ANCA-associated glomerulonephritis.

As shown in Fig. 2, intravenous methylprednisolone pulse therapy was administered every 24 hours for 3 consecutive days; however, on the day following the pulse therapy (Day 5), the patient's respiratory condition suddenly worsened, and she required ventilatory support. DAH was diagnosed on bronchoscopy and chest computed tomography, which showed broad infiltrative shadows and ground glass opacity in her lungs (Fig. 3). Immediately after the diagnosis, plasma exchange was initiated for a total of 7 times for 2 weeks, with approximately 1 time the predicted plasma volume (estimated by the following formula: [0.065×body weight (kg)]×[1-hematocrit]) (11) per session, using freshly frozen plasma as the replacement solution. During this period, water-soluble prednisolone 60 mg (equivalent oral

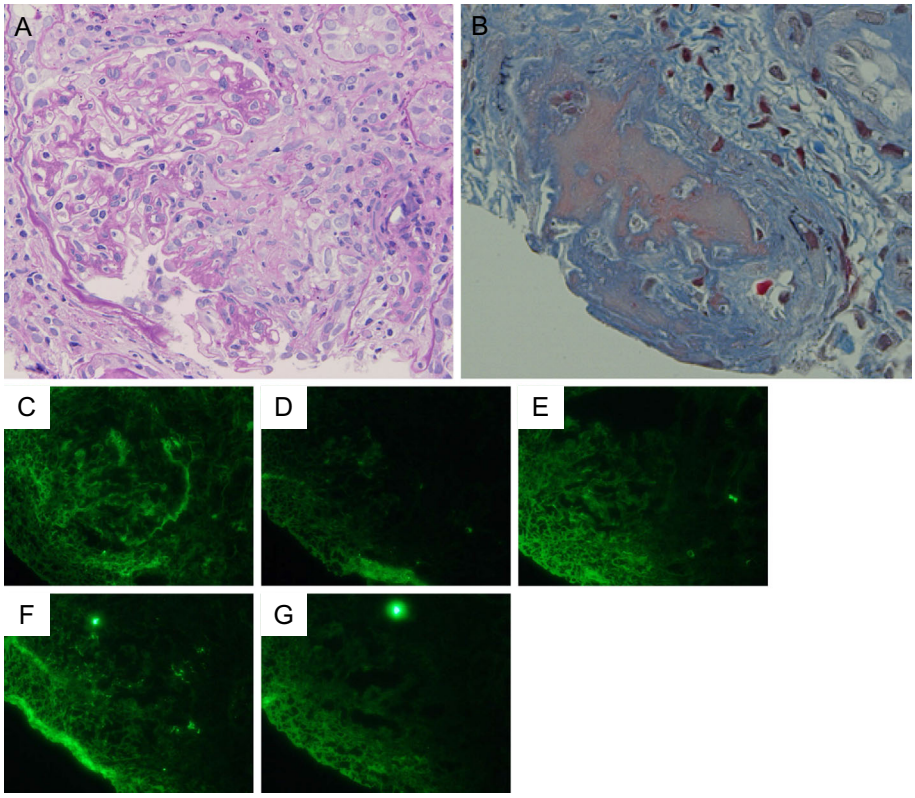

Figure 1. **Histopathology of the kidney. The microscopic findings of the glomerulus showed cellular crescent formation and disruption of the Bowman's capsule (A: periodic acid-Schiff staining; original magnification, ×400). There were few changes in the glomerular basement membrane and mesangial area. High disease activity was indicated by fibrinoid necrosis in the lobular artery (B: Masson's trichrome staining; original magnification, ×400). The immunofluorescence studies revealed no glomerular deposition (C: IgG, D: IgA, E: IgM, F: C3, and G: C1q).**

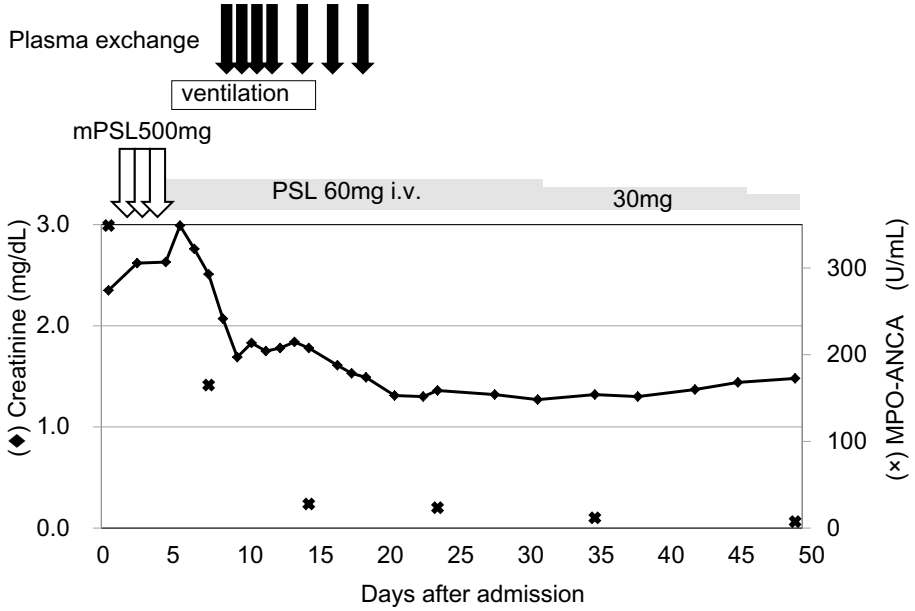

Figure 2. **Clinical course after admission. After admission, methylprednisolone pulse therapy was initiated to treat rapidly progressive glomerulonephritis due to anti-nuclear cytoplasmic antibodies. However, diffuse alveolar hemorrhaging occurred, and the respiratory condition rapidly worsened on Day 5 after admission. Plasma exchange was immediately performed (seven times for two weeks). There was an improvement in the respiratory condition, and the patient was successfully extubated on Day 14. Her serum creatinine level decreased from a maximum of 2.99 mg/dL to 1.48 mg/dL, and the MPO-ANCA titer also decreased to the normal range.**

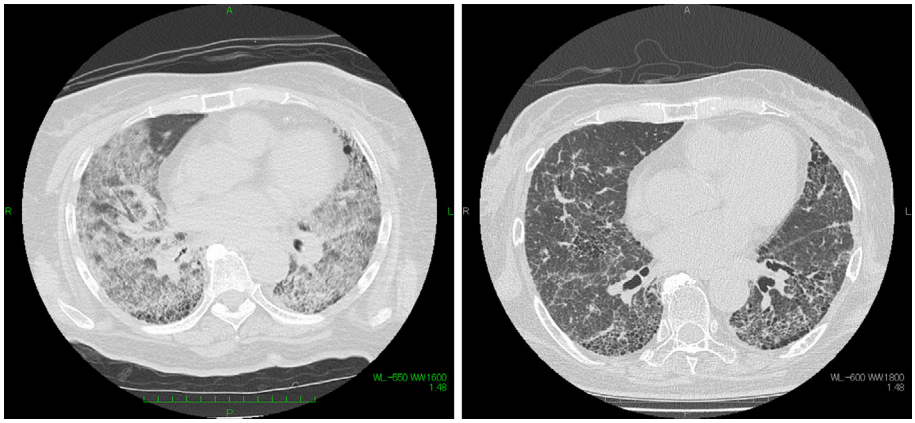

Figure 3. Chest computed tomography. Chest computed tomography on the sudden onset of dyspnea showed broad infiltrative shadows and ground glass opacity in the lungs (left panel). Diffuse alveolar hemorrhaging and acute deterioration of interstitial pulmonary fibrosis was diagnosed. The therapy with plasma exchange and low-dose prednisolone was dramatically effective, and these shadows were considerably attenuated after one month (right panel).

prednisolone dose: 30 mg/day) was administered intravenously.

After 4 sessions of plasma exchange were performed, the FiO_2 decreased from 100% to 30%, and the positive end-expiratory pressure decreased from 10 cmH_2O to 5 cmH_2O. Her respiratory condition improved, and she was successfully extubated on Day 14. The intravenous water-soluble prednisolone was discontinued, and oral prednisolone at a dose of 30 mg per day was started on Day 29. Without using additional immunosuppressive agents, the serum creatinine level returned to 1.48 mg/dL, and the MPO-ANCA titer returned to the normal range. After extubation, the percutaneous oxygen saturation was 100% at rest on 1-2 L of oxygen per minute; however, on exertion, the oxygen saturation dropped to <90%, and she was discharged with home oxygen therapy.

Discussion

We successfully treated an elderly patient with severe AAV and DAH via the immediate introduction of plasma exchange. Therefore, the combination of plasma exchange and low-dose glucocorticoid therapy without additional immunosuppressive agents may be a safe and effective treatment for AAV in elderly patients.

The mortality of AAV is particularly high in cases of critical disease. Mechanical ventilation and admission to the intensive-care unit (ICU) have been reported to be strong predictors of increased mortality within 28 days after admission (12). However, despite requiring mechanical ventilation and ICU admission, the present patient survived. High disease activity and the need for high doses of immunosuppressive agents have also been associated with a higher risk of death, probably due to infection and active vasculitis (13). It is difficult but critically important to achieve an optimal balance of immunosuppression and avoid infection during the treatment of severe AAV.

Although the MPO-ANCA titer had decreased before the initiation of plasma exchange, our patient still required mechanical ventilation and ICU management for DAH. We therefore needed to employ some form of additional therapy and selected plasma exchange. After 4 sessions of plasma exchange were performed, the MPO-ANCA titer decreased from 188 U/mL to 26.2 U/mL. In a previous study, patients with DAH treated by ventilator support needed at least five sessions of plasma exchange for recovery (14). We performed seven sessions of plasma exchange in total, in accordance with the protocol of the ongoing PEXIVAS study (15).

The PEXIVAS study is being conducted to clarify the effectiveness and safety of adjunct plasma exchange and oral glucocorticoid regimens in patients with severe AAV. Patients with AAV accompanied by kidney dysfunction (eGFR <50 mL/min), necrotizing glomerulonephritis, or lung hemorrhage are included in this study and have been randomized to receive one of the following treatment regimens: 1) plasma exchange and either standard or low-dose glucocorticoids or 2) no plasma exchange and either standard or low-dose glucocorticoids. Although the study is still ongoing, Klemmer et al. reported that DAH accompanied by AAV resolved during plasmapheresis in all 20 patients evaluated (14).

According to a previous study (9), 137 newly diagnosed AAV patients with elevated serum creatinine levels were randomly assigned to receive 7 sessions of plasma exchange or 3,000 mg of intravenous methylprednisolone (both groups received oral cyclophosphamide and prednisolone). Most deaths occurred during the first three months, when steroid dosages were the highest and vasculitis was the most active. At three months, however, plasma exchange was associated with a reduction in risk of death and progression to end-stage kidney disease compared with methylprednisolone. Based on these results, we performed combined therapy of 7 plasma exchanges over 2 weeks and methylprednisolone

pulse therapy, followed by low-dose prednisolone (0.5 mg/kg/day) in the present study. Although AAV is commonly treated with oral prednisolone (1 mg/kg/day) in combination with other immunosuppressants, low-dose prednisolone alone was prescribed because of our patient's age and the preceding lung injury. As a result, the disease was controlled with plasma exchange and low-dose prednisolone only, and we succeeded in reducing the risk of treatment-related toxicity, such as infection.

In conclusion, our present findings suggest that the treatment protocol of seven plasma exchanges for two weeks and low-dose prednisolone may be an effective and safe means of inducing the remission of severe AAV in elderly patients.

The authors state that they have no Conflict of Interest (COI).

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