□ CASE REPORT □

Pulmonary-Renal Syndrome, Diffuse Pulmonary Hemorrhage and Glomerulonephritis, Associated with Wegener's Granulomatosis Effectively Treated with Early Plasma Exchange Therapy

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Abstract

We present a case of a 38-year-old Japanese man with Wegener's granulomatosis complicated with pulmonary-renal syndrome, i.e., diffuse pulmonary hemorrhage and rapidly progressive renal glomerulonephritis. As this is a life-threatening condition, we promptly initiated plasma exchange with intravenous methylprednisolone therapy. Diffuse pulmonary hemorrhage and renal failure were markedly improved. This case merits presentation because there are few clinical studies of the treatment of Wegener's granulomatosis with pulmonary-renal syndrome, particularly with pulmonary hemorrhage.

Key words: crescentic necrotizing glomerulonephritis, diffuse pulmonary hemorrhage, plasma exchange, pulmonary-renal syndrome, Wegener's granulomatosis

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Introduction

Wegener's granulomatosis is characterized by small-vessel necrotizing vasculitis and granulomatous inflammation involving mostly the upper and lower respiratory tracts and the kidneys (1). Pulmonary-renal syndrome in Wegener's granulomatosis, defined as a combination of diffuse pulmonary hemorrhage and glomerulonephritis, is a rare but serious complication that carries an extremely high fatality rate (2-5). Therefore, aggressive therapy including intensive immunosuppressive treatment is usually required for the underlying vasculitis.

Case Report

A 38-year-old Japanese man with a 5-month history of persistent serous otitis media was admitted to our hospital because of hemoptysis and renal dysfunction with active urinary abnormalities. One month prior to the admission he had reported constitutional manifestations (i.e., fever, general

myalgia, weight loss), and he had then developed a cough with hemoptysis. He was found to have renal dysfunction with proteinuria and hematuria, progressive anemia, marked inflammatory signs, and an abnormal shadow on chest X-ray. He was therefore referred to our hospital.

On admission, he was in mild distress and complained of slight shortness of breath with frequent cough and hemoptysis, persistent lacrimation in the right eye, bilateral hearing disturbance, and persistent serous nasal discharge. His height was 178 cm, weight was 68.0 kg, temperature was 38.0°C, blood pressure was 160/92 mmHg, pulse rate was 87 beats per minute with regular rhythm, and respiratory rate was 20 times per minute. He had bilateral scleritis and palpable purpura on the lower extremities. Laboratory studies on admission (Tables 1, 2) revealed that he had marked anemia, leukocytosis with eosinophilia, thrombocytosis, abnormal elevations on renal function tests with active urinary abnormalities, and marked elevation of C-reactive protein (CRP). Chest X-ray and computed tomography (CT) scan showed diffuse infiltrates and patchy ground glass opacities in both lung fields (Fig. 1A), and brain CT also showed fluid reten-

Figure 1. Chest CT scans show prompt improvement of diffuse bilateral lung infiltrates and patchy ground glass opacities after the treatment with plasma exchange and corticosteroids. (A) before the treatment; (B) ten days after the treatment. Light microscopic appearance of renal biopsy specimens obtained on day 42 (C and D) shows segmental tuft necrosis and crescents around the glomerular tufts, mild tubular atrophy, interstitial cell infiltration, and interstitial fibrosis (Periodic acid-Schiff stain, C, $\times 40$; D, $\times 200$).

tion in the right maxillary sinus.

Because of hemoptysis, bilateral lung infiltrates, marked anemia, renal dysfunction with active urinary abnormalities, scleritis, palpable purpura, and severe inflammatory signs, we suspected that he had pulmonary-renal syndrome due to systemic vasculitis. Therefore, we promptly initiated a 4-day course of plasma exchange using fresh frozen plasma (3,200 ml per cycle) and a 3-day course of intravenous methylprednisolone (1,000 mg/day) followed by oral prednisolone (PSL) at 50 mg/day. After this therapy his symptoms, including the frequent cough with hemoptysis, persistent lacrimation, nasal discharge and palpable purpura, diminished rapidly, along with a decrease in the level of CRP to the normal range (Fig. 2). On day 7, we obtained a positive result for anti-proteinase 3 (PR3)-anti-neutrophil cytoplasmic antibody (ANCA) (120 EU) and negative results for myeloperoxidase (MPO)-ANCA and anti-glomerular basement membrane antibody. The marked eosinophilia was found on admission, but no histological evidence of granulomatous inflammation could be obtained in our patient; however, our patient had presented persisting unresponsive upper airway involvement, i.e., serous otitis media, followed by sinus inflammation, pulmonary hemorrhage, and rapidly pro-

gressive glomerulonephritis, and he showed a high titer of PR3 ANCA, which has been reported to be highly specific for Wegener's granulomatosis (1). Furthermore, several cases of Wegener's granulomatosis with eosinophilia have been reported (6), and the present patient had reported no history of asthma. For these reasons, we diagnosed our patient as having Wegener's granulomatosis rather than Churg-Strauss syndrome or MPO-ANCA-related microscopic polyangiitis; thus we added oral medication with 50 mg of cyclophosphamide per day. By the tenth hospital day, the diffuse lung infiltration, which was identified by chest CT on admission, had disappeared (Fig. 1B). After 20 days of treatment, his renal function and urinary abnormalities gradually improved and the titer of PR3-ANCA was reduced to 16 EU; tapering of the dosage of PSL was started.

Renal biopsy on day 42 (Figs. 1C, 1D) revealed global sclerosis in 6 glomeruli among the total of 20 glomeruli examined. Segmental tuft necrosis and fibro-cellular crescents were observed in 6 glomeruli. The remaining glomeruli showed minor abnormalities. Mild tubular atrophy, interstitial cell infiltration, and interstitial fibrosis were also observed. Immunofluorescence microscopic examination did not show any deposition of immunoglobulins or comple-

Figure 2. The treatment with plasma exchange and corticosteroids dramatically improved his clinical and laboratory abnormalities. ●, C-reactive protein (CRP, mg/dl); ■, serum creatinine (Cre, mg/dl); mPSL, intravenous methylprednisolone (1,000 mg/day); PE, plasma exchange; PSL, oral prednisolone; CHX, cyclophosphamide.

ments. These findings were compatible with renal pathological lesions associated with Wegener's granulomatosis. As the symptoms and laboratory abnormalities were improved in association with normal urinary findings and decreases in serum creatinine to 1.53 mg/dl and in PR3-ANCA to less than 10 EU, he was discharged on day 70 with treatment with PSL at 35 mg/day and cyclophosphamide at 50 mg/day.

In the outpatient clinic, the dosage of PSL was decreased to 10 mg/day and cyclophosphamide was replaced with azathioprine (50 mg/day) six months after discharge. Two years after discharge, the patient had no symptoms, urinary abnormalities, or signs of recurrence of Wegener's granulomatosis, and he had only mild renal impairment.

Discussion

Here, we describe a patient with Wegener's granulomatosis who showed pulmonary-renal syndrome, i.e., diffuse pulmonary hemorrhage and rapidly progressive renal failure with necrotizing crescentic glomerulonephritis (5). Considering the European Vasculitis Study Group (EUVAS) grading of disease severity, the condition of our patient on admission was thought to be appropriately classified as Severe because of the presence of renal involvement (creatinine concentration, >5.7 mg/dl) and life-threatening disease, i.e., diffuse alveolar hemorrhage (7). Diffuse alveolar hemorrhage is the most serious complication in small-vessel vasculitis, and immunosuppressive therapy alone does not appear to be adequate (3, 4); thus, we promptly started the intensive therapy, plasma exchange with intravenous methylprednisolone therapy, even before the diagnosis of diffuse alveolar hemorrhage associated with Wegener's granulomatosis was confirmed with histological or immunological examinations. This treatment dramatically improved his respiratory symp-

Table 1. Laboratory Data on Admission

Arterial blood gases (under room air)	
pH	7.422
PaO ₂ (mmHg)	80.5
PaCO ₂ (mmHg)	30.5
HCO ₃ (mEq/l)	20.2
Urinalysis	
Protein	3+ (daily proteinuria, 2.0 g)
Occult blood	3+
Sugar	—
Sediments	
Erythrocytes (/HPF)	100-200
Leukocytes (/HPF)	10-20
Granular casts	Many
Peripheral blood	
Hematocrit (%)	24.0
Hemoglobin (g/dl)	7.5
Red blood cells (μl)	3,100,000
White blood cells (μl)	12,400
Eosinophils (μl)	3,900
Platelets (μl)	553,000
Blood chemistry	
Total protein (g/dl)	6.8
Albumin (g/dl)	3.5
AST (IU/l)	11
ALT (IU/l)	11
Lactate dehydrogenase (IU/l)	188
Alkaline phosphatase (IU/l)	190
Total bilirubin (mg/dl)	0.61
CPK (IU/l)	44
Sodium (mEq/l)	135
Potassium (mEq/l)	5.4
Chloride (mEq/l)	94
Blood urea nitrogen (mg/dl)	70.3
Creatinine (mg/dl)	6.2
Uric acid (mg/dl)	9.6
Calcium (mg/dl)	9.2
Phosphate (mg/dl)	6.4

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; HPF, high-power field.

toms, i.e., cough and hemoptysis, and the diffuse lung infiltrates identified with chest CT. Because of these circumstances, we could not perform bronchoscopy to obtain the histological evidence of alveolar hemorrhage, i.e., hemosiderin-laden alveolar macrophages in bronchoalveolar lavage fluid (7).

In Wegener's granulomatosis, 75% to 90% of patients with active disease have PR3-ANCA (1). The role of PR3-ANCA in the pathogenesis of this disease is still controversial, but in vitro evidence suggests that PR3-ANCA can directly or indirectly damage endothelial cells (8). Once the endothelial cells are damaged in the vasculitis lesions, the red blood cells, as well as other plasma products, escape into extravascular spaces, i.e., the Bowman's space of the glomerulus or alveolar spaces of the lung, which causes the formation of crescentic glomerular lesions or pulmonary hemorrhage, respectively. Therefore, plasma exchange is thought to be effective for pulmonary-renal syndrome due to ANCA-related small-vessel vasculitis (e.g., microscopic polyangiitis and Wegener's granulomatosis), because it can quickly remove the ANCAs and inflammatory mediators from the circulation. Indeed, an ongoing European MEPEx (methylprednisolone vs plasma exchange as additional therapy for severe ANCA-associated glomerulonephritis) trial

Table 2. Serological Test Data on Admission

IgG (mg/dl)	1324
IgM (mg/dl)	177
IgA (mg/dl)	348
C3 (mg/dl)	113
C4 (mg/dl)	23
CRP (mg/dl)	14.93
MPO-ANCA (EU)	< 10 EU
GBM antibody	Negative
ANA	1:40
PR3-ANCA (EU)	120

ANA, antinuclear antibody; C3, complement 3; C4, complement 4; CRP, C-reactive protein; GBM, glomerular basement membrane; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody; PR3-ANCA, anti-protease 3-anti-neutrophil cytoplasmic antibody.

has shown a benefit of plasma exchange for severe renal vasculitis at 3 months (9).

The pulmonary hemorrhage in the present patient resolved immediately and completely by 10 days after the induction of this intensive therapy with a concomitant decrease of PR3-ANCA titers, while the renal abnormalities such as necrotizing glomerulonephritis had persisted even after the 6-week treatment. Although necrotizing capillaritis is the common pathological feature of diffuse pulmonary hemorrhage and crescentic glomerulonephritis in ANCA-related small-vessel vasculitis (7), our study seems to suggest that the necrotizing capillaritis in the lung is more sensitive to the intensive therapy than that in the kidney.

There have been, however, few studies focusing on the use of plasma exchange to treat pulmonary-renal syndrome of ANCA-related small-vessel vasculitis (4, 5, 9-11). Falk et al have reported in an observation study that plasma exchange reduced mortality by 50% in patients with small-vessel vasculitis who had pulmonary hemorrhage (4). Gallagher et al treated 12 of 14 pulmonary-renal syndrome patients with plasma exchange with on average 6.1 treatments,

with only 1 death from active vasculitic disease (5). Klemmer et al have reported a retrospective uncontrolled study of 20 patients with ANCA-related small-vessel vasculitis who presented with diffuse pulmonary hemorrhage and were treated with plasma exchange (10). The diffuse pulmonary hemorrhage was resolved in all 20 patients with on average 6.4 plasma exchanges with 5% albumin and fresh frozen plasma as the replacement fluids. Conversely, the study of the Japanese RPGN registry has revealed that apheresis treatment was performed in only 26.6% of the patients with pulmonary-renal syndrome, resulting in a poor prognosis (11). However, these clinical studies have included only a few patients with Wegener's granulomatosis [number of Wegener's granulomatosis patients /total number of patients in each study: 0/14(5), 2/20 (10), 0/79 (11)]. Several anecdotal case reports have shown that plasma exchange can dramatically improve diffuse pulmonary hemorrhage in the patients with Wegener's granulomatosis as in the present case (12, 13), but the treatment protocol of plasma exchange, i.e., indications, modality of plasma exchange, treatment plasma volume, duration, and replacement fluids (albumin or frozen plasma), remains to be determined.

Plasma exchange is mentioned as a treatment for vasculitis-related pulmonary hemorrhage in the textbooks of internal and pulmonary medicine (14), but conventional utilization of plasma exchange in the treatment of pulmonary-renal syndrome including pulmonary hemorrhage complicated with Wegener's granulomatosis has been supported by only a few uncontrolled observation studies. As diffuse pulmonary hemorrhage is a life-threatening condition, it might be difficult to perform controlled clinical trials. The present study shows the possibility of the effectiveness of plasma exchange in the treatment of pulmonary-renal syndrome in Wegener's granulomatosis; therefore, further accumulation of clinical studies including case reports is necessary to confirm the usefulness of plasma exchange for this critical condition.

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