



Case report

Successful treatment of steroid-refractory double-positive ANCA and anti-GBM disease with a combination of plasma exchange and immunosuppression: A case report and literature review

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ABSTRACT

The concurrence of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and anti-glomerular basement membrane (GBM) disease, known as double-positive disease, is rare, but it occurs at a much higher frequency than expected by chance. Double-positive disease has an aggressive clinical course, with no optimal treatment strategy. Here we describe a patient with steroid-refractory double-positive disease who was treated successfully with the addition of plasma exchange (PE) and cyclophosphamide (CPA). A 78-year-old Japanese woman who was diagnosed with diffuse alveolar hemorrhage and rapidly progressive glomerulonephritis received two cycles of pulse steroid therapy. However, her respiratory and renal condition deteriorated. She was found to be positive for both myeloperoxidase-ANCA and anti-GBM antibodies. The combination of PE and CPA improved her systemic condition. This is the first case report of a patient with steroid-refractory double-positive disease who was successfully treated with the addition of PE and CPA. The marked contrast in therapeutic response to corticosteroids alone and the addition of PE and CPA in this case strongly implies that earlier induction of combination therapy aimed at rapid removal of pathogenic autoantibodies and prevention of ongoing antibody production might improve the outcome of this life-threatening disease.

1. Introduction

Anti-glomerular basement membrane (GBM) disease and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are each clinically associated with the development of rapidly progressive glomerulonephritis (RPGN) and diffuse alveolar hemorrhage (DAH) [1,2]. These diseases are rare, but are associated with an increased risk of morbidity and mortality from renal or respiratory failure. Anti-GBM disease is an immune complex small vessel vasculitis affecting glomerular and pulmonary capillary beds with anti-GBM antibody deposition in the basement membrane. AAV is a necrotizing vasculitis with few or no immune deposits, predominantly affecting small vessels associated with ANCAs specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) [1–3]. The concurrence of ANCA and anti-GBM disease, known as double-positive disease, is an extremely rare condition, but it is recognized to occur at a much higher frequency than expected by chance. Patients who are double-positive account for approximately half of all patients with anti-GBM disease. Approximately 10% of patients with AAV are reported to also have anti-

GBM antibodies [4–6]. The relatively high concurrence rate for ANCA and anti-GBM disease and worse prognosis of patients with double-positive disease compared to those of patients with either ANCA or anti-GBM alone [7] suggest that these two conditions might synergistically impact disease initiation and progression. At present, there is no optimal treatment strategy for double-positive disease.

Here we report a patient with steroid-refractory double-positive disease treated successfully with a combination of plasma exchange (PE) and cyclophosphamide (CPA). The distinct therapeutic responses to corticosteroids and PE/CPA in the present case might provide important information about therapeutic strategies for this life-threatening disorder as well as better understanding of the pathogenesis of this complex autoimmune disease.

2. Clinical report

A previously healthy 78-year-old Japanese woman with a 3-month history of hemoptysis visited a primary care physician. She had never smoked and had no history of alcohol use. She did not take any

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Fig. 1. Computed tomography on arrival at our hospital showed diffusely distributed ground-glass opacities in both lung fields.

medications or dietary supplements routinely. Laboratory data included a white blood cell count of 12,500/ μ L. Her chest radiograph showed infiltrative shadows in the lower lung fields bilaterally. She was initially treated with oral azithromycin and intravenous meropenem for 7 days; however, the infiltrative shadows expanded and she developed acute respiratory failure. Chest computed tomography (CT) showed diffusely distributed ground-glass opacities in both lung fields (Fig. 1). Bronchoscopy revealed active bleeding from the superior segmental bronchus of both lungs. She was diagnosed with DAH and treated with 2 cycles of pulse methylprednisolone therapy (1000 mg IV daily for 3 consecutive days). However, on hospital day 11, her respiratory and renal condition deteriorated. She was referred to our hospital.

Physical examination at the time of transfer showed that her body temperature was 37.3 °C, blood pressure was 144/63 mmHg, pulse was 60 beats per minute, oxygen saturation was 95% with oxygen supplementation at 12 L/min via a mask with reservoir bag, and respiratory rate was 32 breaths per minute. Her Glasgow Coma Scale score was 14 (4 for eyes, 4 for verbal, 6 for motor score). Lung auscultation revealed decreased breath sounds in the right lower lung field. The abdominal and cardiac examinations were normal. Laboratory data included an urine protein level 1+, uric acid level 3+, a white blood cell count of 21,400/ μ L with 97.8% neutrophils, hemoglobin of 10.3 g/dL, blood urea nitrogen of 48.3 mg/dL, creatinine of 1.11 mg/dL, and lactate dehydrogenase of 337 U/L. Arterial blood gas analysis showed severe type 1 respiratory failure. In addition, she was positive for both MPO-ANCA and anti-GBM antibodies (52.7 U/mL and 13.5 U/mL, respectively). Other data are shown in Table 1.

We could not perform any histological examinations because of her poor systemic condition. Her renal function deteriorated rapidly, with proteinuria and hematuria. We clinically diagnosed RPGN. Given the context of DAH, RPGN, and double-positivity for MPO-ANCA and anti-GBM antibodies, she was diagnosed with double-positive disease.

The patient underwent mechanical ventilation, vasopressor therapy, and continuous hemodiafiltration. Based on the diagnosis of double-positive disease, we added intravenous CPA (560 mg/day, single injection, then changed to oral administration on day 37, 75 mg/day) and PE (7 times every 2 weeks, total 14 times). She also received prednisolone, tapered from a maximum starting dose of 50 mg/day. Afterwards, her systemic condition gradually improved (Fig. 2). She had an uncomplicated hospital course and was successfully weaned from mechanical ventilation on day 32. MPO-ANCA levels decreased from 52.7 U/mL on day 11 to 6.1 U/mL on day 35, and anti-GBM antibody levels normalized on day 35. She improved clinically and was

transferred to her previous doctor for rehabilitation on day 79. Chest CT 52 days after discharge showed substantial resolution of the ground-glass opacities. At 96 weeks after discharge with oral prednisolone therapy (4 mg/day), she was asymptomatic with normal serum levels of anti-GBM and MPO-ANCA antibodies.

3. Discussion

This is the first case report of a patient with steroid-refractory double-positive disease who was successfully treated with the addition of PE and CPA. The marked contrast in therapeutic response between corticosteroids alone and the addition of PE and CPA in this case strongly implies that earlier induction of combination therapy in double-positive disease aimed at rapid removal of pathogenic auto-antibodies and prevention of ongoing antibody production might improve outcomes.

Anti-GBM antibodies play a major role in the pathogenesis of anti-GBM disease. They target the noncollagenous domain 1 of the α 3 chain of type IV collagen [α 3(IV)NC1], which has two major epitopes, E_A and E_B, found in the basement membrane specific to the glomerulus and alveolus [8,9]. With regards to the pathogenesis of AAV, B cell-derived ANCAs cause neutrophil activation and subsequent endothelial damage [10]. B cell depletion is associated with lower circulating ANCA levels and clinical remission in the majority of patients with AAV, strongly implicating that ANCAs are involved in the pathogenesis of AAV. Co-presentation with both anti-GBM antibodies and ANCAs appears more commonly than expected, as described above, although the mechanisms underlying the association between ANCAs and anti-GBM antibodies and the possible common pathogenic mechanisms remain unclear. No cross-reactions have been demonstrated between ANCAs and anti-GBM antibodies at the B-cell level; these two antibodies are antigenically distinct [11,12]. Several lines of evidence indicate that double-positive disease exhibits a more aggressive clinical course than either anti-GBM or AAV alone. Patients with double-positive disease require renal replacement therapy more frequently than patients with either anti-GBM disease or AAV alone [7,13]. In addition, serum creatinine levels in double-positive disease are higher than in either anti-GBM disease or AAV alone [6,7]. Our patient required renal replacement therapy at presentation. Furthermore, in one study, none of the double-positive patients with severe renal failure at presentation recovered renal function despite immunosuppression with or without PE [5]. This is in stark contrast to patients with pure AAV who present with a need for dialysis, of whom 75% recover renal function [14]. These findings suggest that double-positive disease is truly a hybrid disease phenotype and the aggressive features of double-positive disease may reflect more severe glomerular and alveolar damage due to an anti-GBM-mediated mechanism, in addition to ANCA-mediated endothelial disruption.

With regards to the mechanisms that initiate double-positive disease, almost all patients with anti-GBM disease have detectable levels of MPO-ANCA or PR3-ANCA before disease onset [15]. In addition, as seen in the present case, the duration of symptoms before diagnosis is similar for AAV and double-positive disease (median, 10–12 weeks), but is significantly longer than for single-positive anti-GBM disease (median, 2 weeks) [7]. Furthermore, double-positive patients have more features of chronicity on renal biopsy compared with patients with single-positive anti-GBM disease [7]. These findings suggest that ANCAs trigger endothelial injury and patients develop anti-GBM responses through the modification or exposure of originally sequestered disease epitopes in the GBM. This would explain why double-positive patients have anti-GBM antibodies with broader reactivity [16]. However, if so, it is unusual that only 10% of patients with AAV have anti-GBM disease. At present, it is not fully understood whether AAV predisposes to the development of anti-GBM disease or whether ANCA production occurs during the progression of anti-GBM disease. Further investigations are needed to elucidate the precise pathogenesis of double-positive disease.

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