AP-VAS 2012 case report: anti-glomerular basement membrane disease with high titer of myeloperoxidase anti-neutrophil cytoplasmic antibody—an autopsy case report

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Received: 4 September 2012 / Accepted: 7 January 2013 / Published online: 10 April 2013
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Abstract It has been reported that patients who are positive for both myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) and anti-glomerular basement membrane (GBM) antibody have a poor prognosis. We present an autopsy case of anti-GBM disease with a high titer of MPO-ANCA. The patient was a 77-year-old woman with a medical history of idiopathic interstitial pneumonia. After being treated for bacterial pneumonia, she was referred to our hospital for evaluation of non-nephrotic range proteinuria, hematuria, and a course of rapidly progressive glomerulonephritis. Results of urinalysis were 2+ for protein and 3+ for blood, with many dysmorphic red blood cells observed in the urinary sediment. A sample of a 24-h urine collection contained 0.3 g protein. The serum creatinine concentration was 5.0 mg/dl on admission. The patient tested positive for MPO-ANCA at a titer of >640 EU and for anti-GBM antibody at a titer of 14 EU. Renal biopsy revealed glomerulonephritis with crescent formation, and immunofluorescence studies showed that the glomeruli had a generalized linear

fluorescence and anti-immunoglobulin G (IgG) and C₃ along the peripheral glomerular capillaries. She was diagnosed with anti-GBM disease. Treatment was started with intravenous prednisolone and oral cyclophosphamide, followed by plasma exchange. Despite improved renal function, she died of pulmonary hemorrhage. Autopsy revealed deposits of IgG and C₃ in the basement membranes of lung alveoli.

Keywords Anti-GBM antibody · MPO-ANCA · RPGN · Pulmonary-renal syndrome · Idiopathic interstitial pneumonia

Introduction

Anti-glomerular basement membrane (GBM) disease is a rare autoimmune disorder associated with rapidly progressive glomerulonephritis (RPGN) and pulmonary hemorrhage. On the other hand, myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) is commonly manifested as RPGN in association with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA). It has been reported that patients positive for both MPO-ANCA and anti-GBM antibody have a higher mortality than those positive for anti-GBM antibody alone, as well as having a poorer renal outcome [1]. We present here the autopsy case of a patient who tested positive for both of these antibodies.

Case report

A 77-year-old female who had smoked 20 cigarettes per day for 48 years visited our hospital because of abnormal

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opacities on the chest X-ray in June 2006. She had a prior history of gastroesophageal reflux disease. A clinical diagnosis of idiopathic pulmonary fibrosis was made and she was followed up without treatment. In February 2009, she had pneumonia and received antibiotic therapy. Her renal function was unremarkable until May 2009, when hematuria and a serum creatinine (Cr) level of 1.3 mg/dl were found. She was admitted to the nephrology department for evaluation of RPGN. The physical examination was notable for the presence of fine crackles at the base of both lungs. There was no leg edema, rash, or clubbing. Urinalysis showed hematuria 3+, proteinuria 2+, red blood cells at 30–49/HPF, white blood cells at 20–29/HPF, and granular cast 1+. Serum Cr was 5.0 mg/dl. C-reactive protein was 4.6 mg/dl. Immunological tests showed the patient was positive for antinuclear antibody, MPO-ANCA (>640 EU), and anti-GBM antibody (14 EU/ml), but negative for other autoimmune antibodies including proteinase 3-ANCA. Serum KL-6 and SP-D levels were 413 (normal <500) U/ml and 51.7 (normal <110) ng/ml, respectively. Reticular shadows in the bilateral lower lung fields were visible on the chest X-ray. High-resolution computed tomography (CT) scan of the chest showed linear opacities with honeycombing in the lower lobes of both lungs.

We started methylprednisolone pulse therapy (1 g/day for 3 days), followed by oral prednisolone 40 mg/day (1.0 mg/kg/day) and oral cyclophosphamide (50 mg/day) for RPGN. An open renal biopsy performed on day 49 showed diffuse crescentic glomerulonephritis, with immunofluorescence studies revealing linear capillary wall staining for immunoglobulin G (IgG) and C₃ (Fig. 1a–c). There were no granuloma or extraglomerular vasculitis. Based on these findings the patient was diagnosed with anti-GBM disease. She developed dyspnea on day 69, and bilateral diffuse ground-glass opacities appeared in addition to bilateral fibrosis on her chest CT. Her CRP was as high as 13 mg/dl. A bronchoalveolar lavage examination showed pulmonary hemorrhage, suggesting acute exacerbation of anti-GBM antibody disease. She was treated with steroid pulse therapy, plasma exchange, and mechanical ventilation. We considered the activity of anti-GBM antibody disease was weakened because her CRP decreased to 0.2 mg/dl after the sixth plasma exchange, and she was extubated on day 80 as shown in Fig. 2. However, respiratory failure progressed, complicated with sepsis by *Staphylococcus epidermidis*, and the patient died on day 91 despite antibiotic therapy.

At autopsy, the lungs showed thickening of alveolar septa and honeycomb change with infiltration of inflammatory cells (Fig. 3a). Hyaline membranes lining airspaces and interstitial edema were also observed. IgG and C₃ were detected in the alveolar walls by immunofluorescence (Fig. 3b, c). There was no evidence of infection of

Pneumocystis jiroveci. Almost all kidney glomeruli showed fibrous crescents, and the glomerular tufts were collapsed. There was no evidence of *Cytomegalovirus* infection in the intestine. There was no evidence of infection or vasculitis in other organs.

Discussion

Anti-GBM antibody disease is caused by autoantibodies against the noncollagenous region of the alpha 3 chain of type 4 collagen [2]. Factors implicated in triggering anti-GBM disease include smoking, infections, previous hydrocarbon exposure, primary glomerular diseases, and cocaine abuse [3].

Specifically, the presence of MPO-ANCA can produce oxidants, which increase proteolysis of the GBM [4]. Meli et al. reported that matrix metalloproteinase-9, which can be activated by MPO, is able to cleave the epitope of the disease. Thus, the presence of MPO-ANCA leads to the possibility of damage to the GBM.

The patient had pneumonia approximately 3 months before the onset of RPGN, and this infection might have induced MPO to develop on the surface of neutrophils. MPO reacts with ANCA and leads to the activation of neutrophils. This endothelial damage by ANCA could expose antigens in the capillary walls in both lungs and kidneys and release alveolar or GBM antigens into the circulation, resulting in the production of anti-GBM antibodies [5]. In the case of our patient, her past smoking history of about 50 years may have influenced the onset of anti-GBM antibody disease. Yashiro et al. [6] reported that regional morbidity of MPO-ANCA-related angitis increased after the Great Kobe Earthquake (Japan) of 1995. These authors suggest that severe air pollution caused by the earthquake was responsible for the high frequencies of upper respiratory tract inflammation as an initial symptom and severe pulmonary involvement. Silica is known to be a causative agent of ANCA-related glomerulonephritis, possibly activating alveolar macrophages, resulting in inflammatory reactions and chemotaxis of neutrophils. The onset ANCA-related glomerulonephritis may be related to the earthquake because our patient survived this earthquake in Kobe.

Based this information and the medical history of our patient, we suggest the following sequence may be considered in this case. Severe air pollution due to the Great Kobe Earthquake initially stimulated MPO-ANCA, which caused pulmonary fibrosis. Then, infection stimulated MPO-ANCA once again, resulting in damage to pulmonary membranes and GBMs and the production of anti-GBM antibody.

It has been reported that 22–38 % of patients with anti-GBM antibodies also have detectable ANCA [7, 8] and that

Fig. 1 **a** Crescent formation is seen in about 60 % of all glomeruli. Masson trichrome stain, $\times 40$. **b, c** Staining of immunoglobulin G (IgG) (**b**) and C_3 (**c**) showing linear global glomerular capillary wall positivity, $\times 40$

Fig. 2 Clinical course. BAL Bronchoalveolar lavage, CMV Cytomegalovirus, CPA cyclophosphamide, CRP C-reactive protein, GBM ab glomerular basement membrane antibody, MCFG micafungin, MPO-ANCA myeloperoxidase anti-neutrophil cytoplasmic antibody, NPPV noninvasive positive-pressure ventilation, PSL prednisolone, SBT/CPZ sulbactam/cefoperazone, VCM vancomycin

Fig. 3 **a** Shown are edema of the alveolar septa and formation of hyaline membranes that line the alveolar spaces. Hematoxylin and eosin stain, $\times 40$. **b, c** Staining of IgG (**b**) and C_3 (**c**) revealing linear alveolar wall positivity, $\times 40$

the mortality rate of such double-positive patients is higher than that in patients positive for only anti-GBM antibody [1, 7]. In one study, the survival rate of patients positive for both anti-GBM antibodies and ANCA at 1 year was 48.7 %, which is poorer than that of patients positive for anti-GBM antibody only (79.6 %) ($p < 0.001$) [7]. In other studies, the renal outcome of double-positive patients was similar to that of patients with anti-GBM disease [9, 10]. However, Rutgers et al. [1] showed that double positivity is also related to a poorer prognosis. Clearly, more cases will need to be collected and analyzed.

This case was diagnosed as idiopathic pulmonary fibrosis which subsequently developed into RPGN and pulmonary hemorrhage. Of the 103 double-positive cases identified in our search in Japan, there were eight cases (7.8 %) of interstitial pneumonia. Arimura et al. [11] reported that about 10 % of the total pulmonary fibrosis or interstitial pneumonitis cases in Japan were due to MPO-ANCA-associated vasculitis. Moreover, about 60 % of MPO-ANCA-associated vasculitis patients presented initially with pulmonary features (mostly pulmonary fibrosis). We suggest that pulmonary fibrosis may be a result of damage to the capillary walls by MPO-ANCA. However, most of the cases we identified were not examined for MPO-ANCA or anti-GBM antibody at the time when the patients had pulmonary fibrosis. An examination for vasculitis should be considered in pulmonary fibrosis patients.

In conclusion, we present a rare case of a patient who tested positive MPO-ANCA and anti-GBM antibody and had a poor prognosis. Simultaneous screening for ANCA should be performed in patients with anti-GBM antibody.

Conflict of interest None.

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