Goodpasture's Syndrome Associated with Primary Biliary Cirrhosis

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A 73-year-old woman who had a history of primary biliary cirrhosis developed rapidly progressive glomerulonephritis and pulmonary-renal syndrome. She was found to have anti-mitochondrial antibody (AMA) and myeloperoxidase (MPO) anti-neutrophil cytoplasmic antibody (ANCA). She also had weak anti-glomerular basement membrane (GBM) antibody. She was treated with methylprednisolone pulse therapy, but died of respiratory failure. On postmortem examination, both lungs showed diffuse hemorrhage and the immunofluorescence study of the kidney revealed linear immunoglobulin G (IgG) deposition along the glomerular basement membrane.

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Key words: myeloperoxidase (MPO)- anti-neutrophil cytoplasmic antibody (ANCA), anti-mitochondrial antibody (AMA), anti-glomerular basement membrane (GBM) antibody, crescentic glomerulonephritis, pulmonary-renal syndrome

Introduction

Although Goodpasture's syndrome is rare in Japan, many cases of pulmonary-renal syndrome have been reported. Such pulmonary-renal syndromes are thought to be anti-neutrophil cytoplasmic antibody (ANCA)-related. Myeloperoxidase (MPO)-ANCA often coexists with other autoantibodies, including anti-glomerular basement membrane (GBM) antibody (1, 2). Primary biliary cirrhosis (PBC), on the other hand, is an autoimmune disease rarely found to have ANCA. In this report, we describe a case of Goodpasture's syndrome associated with MPO-ANCA and anti-GBM antibody that developed in a 73-year-old woman who has a history of PBC.

Case Report

A 73-year-old woman was admitted to Shizuoka City Hospital on December 11, 1996, because of anuria and worsening renal function. In August 1996, she was in the same hospital because of compression fracture of vertebral bone. For many years she had been known to have chronic liver disease, but the disease proved to be PBC when she was found to have anti-mitochondrial antibody (AMA) and an increased level of alkaline phosphatase. Her renal function was normal. As her PBC was asymptomatic, she was prescribed ursodesoxycholic acid and sent for rehabilitation to another hospital. On November 17,

she was found to have macrohematuria and proteinuria without preceding episode of infection or exposure to chemicals. A few days later, her face and extremities became edematous. On December 7, her urine volume decreased, and laboratory studies disclosed abnormal renal function. On December 11, the temperature increased to 38.4°C and she came back to our hospital.

On physical examination she looked pale and dyspneic. Her temperature was 37.9°C, blood pressure was 144/44 mmHg, and pulse was 90. The respirations were 30. Coarse rhonchi and crackles were heard over her entire chest wall and largely obscured the heart sounds. The abdomen was soft and her lower extremities were edematous. No rash or lesions indicative of vasculitis were seen. A specimen of arterial blood, drawn while she was breathing room air, disclosed partial pressure of oxygen (PaO₂) 53.4 mmHg, partial pressure of carbon dioxide (PaCO₂) 34.7 mmHg, and the pH 7.415. Radiographs of the chest revealed diffuse opacification of both lungs and there was a small amount of pleural effusion. Electrocardiogram showed sinus tachycardia. Abdominal echography showed that bilateral kidneys were normal and hydronephrosis was not present. Laboratory studies are shown in Table 1.

She was thought to have acute renal failure with heart failure, and an emergent hemodialysis was begun. But even after hemodialysis radiographic findings of the chest were not improved, and PaO₂ was 58.9 mmHg while she was breathing 2 //

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Table 1. Laboratory Data on Admission

Peripheral blood		Urinalysis	
White blood cell	8,900/ μ l	pH	6.0
Red blood cell	308×10^4 / μ l	Protein	(2+)
Hemoglobin	8.1 g/dl	Occult blood	(3+)
Hematocrit	24.9%	Sugar	($\pm$)
Platelet	40.3×10^4 / μ l	Urobilinogen	($\pm$)
Coagulation		RBC	>100/HPF
Prothrombin time	9.7 s	WBC	10~19/HPF
Activated partial thromboplastin time	31.1 s	Granular cast	(+)
Fibrinogen	186.6 mg/dl	Creatinine clearance	1.0 ml/min
Fibrin degradation product	17.4 μ g/ml	Urine protein	1.16 g/day
Serology		Blood chemistry	
Immunoglobulin G	1,699 mg/dl	Total protein	5.8 g/dl
Immunoglobulin A	374 mg/dl	Albumin	2.2 g/dl
Immunoglobulin M	344 mg/dl	Blood urea nitrogen	77 mg/dl
C3	79 mg/dl	Creatinine	7.5 mg/dl
C4	29 mg/dl	Uric acid	5.4 mg/dl
CH50	35.9 U/ml	Glucose	102 mg/dl
Immunology		Total bilirubin	0.3 mg/dl
Anti-nuclear antibody	(-)	Aspartate aminotransferase	20 U/l
Rheumatoid factor	56 U/ml	Alanine aminotransferase	8 U/l
Cryoglobulin	(-)	Alkaline phosphatase	300 U/l
MPO-ANCA	394 EU	Lactate dehydrogenase	609 U/l
C-ANCA	<10 EU	Creatine phosphokinase	45 U/l
Anti-GBM antibody	14 EU	Total cholesterol	251 mg/dl
AMA	$\times 256$	Na	134 mEq/l
		K	4.4 mEq/l
		Cl	106 mEq/l
		Ca	7.8 mg/dl
		Pi	5.4 mg/dl
		C reactive protein	7.1 mg/dl

MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, Anti-GBM antibody: anti-glomerular basement membrane antibody, AMA: anti-mitochondrial antibody.

min oxygen. We considered the possibility of rapidly progressive glomerulonephritis with pulmonary-renal syndrome, so she had methylprednisolone pulse therapy (500 mg/day, for 3 days). On December 16, cyanosis developed and an endotracheal tube was inserted. Blood-tinged sputa often spouted. On December 18, we knew that MPO-ANCA was positive ($\times 394$) and anti-GBM antibody was slightly elevated ($\times 14$), but her general status was so bad that we could not attempt plasmapheresis therapy. She died of respiratory failure on December 20.

An autopsy was performed. The renal findings included crescentic glomerulonephritis, with over 90% of the glomeruli showing crescents (Fig. 1). Most of the crescents were fibrocellular, and there was diffuse tubular atrophy. Immunofluorescence study revealed linear staining of the GBM for immunoglobulin G (IgG) (Fig. 2). Crescents were also stained for fibrin related antigen. Histologic examination of the lung revealed blood-filled alveoli and hemosiderin-laden macrophages. Immunological study showed staining of the alveolar basement membrane for IgG. The liver specimen was

Figure 1. Light microscopic examination revealed crescentic glomerulonephritis with over 90 % of the glomeruli showing crescent formation (PAS stain, $\times 200$).

Figure 2. Immunofluorescence study revealed linear staining of the glomerular basement membrane for IgG ($\times 400$).

sent to Kansai Medical University for the evaluation of PBC. According to the report, the liver change was consistent with PBC (stage II). There were no changes indicative of systemic vasculitis in other organs, such as skin, nerves, and gastrointestinal tract.

Discussion

The main feature of this case report is pulmonary-renal syndrome which can be attributed either to anti-GBM antibody or to MPO-ANCA. The titer of anti-GBM antibody was low but the histological appearance of linear IgG deposition strongly suggested that crescentic glomerulonephritis and pulmonary hemorrhage were related to anti-GBM antibody. Since the coexistence of anti-GBM antibodies and ANCA is widely recognized (1, 2), it does not seem to be meaningful to discuss which of the two antibodies played a dominant role in this case (3). Autopsy revealed pulmonary hemorrhage and no systemic vasculitis, so we thought this case was Goodpasture's syndrome.

Although the clinical course was very rapidly progressive, we could attempt plasmapheresis therapy when we considered the possibility of pulmonary-renal syndrome. However, it was

too late when we learned that the tests for MPO-ANCA and anti-GBM antibody were positive. It may be helpful to attempt plasmapheresis therapy together with steroid pulse therapy when a patient shows rapidly progressive glomerulonephritis with pulmonary-renal syndrome.

What is unique to our patient is that she had a long history of chronic liver disease and that AMA was positive. Patients with PBC often have other auto-immune diseases, such as Sjögren's syndrome, chronic thyroiditis, and rheumatoid arthritis (4), but the association of PBC with pulmonary-renal syndrome has not been recognized. MPO-ANCA was described in sera from a patient with PBC (5), but the reported patient did not develop ANCA-related vasculitis. Therefore, the pathogenetic importance of ANCA in the development of PBC is not established (6, 7). In this case, there is clinical and histological evidence that she actually developed both pulmonary-renal syndrome and PBC. Since the onset of pulmonary-renal syndrome does not seem to be close to the onset of PBC, it may not be convincing to say that PBC could be complicated with pulmonary-renal syndrome or ANCA-related vasculitis. An autoimmune mechanism is assumed in the development of those diseases, however, it is likely that immunological disturbance which activated AMA may influence the subsequent development of pulmonary-renal syndrome.

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