Goodpasture’s Syndrome: A Report of an Autopsy Case and a Review of Japanese Cases

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A 75-yr-old man was admitted because of acute renal failure. On the 9th hospital day, pulmonary hemorrhage occurred. He was treated with a bolus dose of methylprednisolone and plasma exchange, but died from respiratory failure on the 16th hospital day. Autopsy findings demonstrated marked intraalveolar hemorrhage and crescentic glomerulonephritis. Linear depositions of IgG along both alveolar and glomerular basement membranes (GBM) were shown by direct immunofluorescent studies. Circulating anti-GBM antibodies were demonstrated by indirect immunofluorescent techniques. This is a confirmatory case of Goodpasture’s syndrome, which is rare in Japan. A review of the Japanese literature revealed some characteristics of Japanese cases.

Key words: anti-glomerular basement membrane antibody, crescentic glomerulonephritis, pulmonary hemorrhage

Introduction

Goodpasture’s syndrome is defined as an autoimmune disorder consisting of the following three essential criteria: 1) pulmonary hemorrhage, 2) glomerulonephritis, commonly of a rapidly progressive or crescentic form, and 3) circulating antibody formation against alveolar and glomerular basement membranes (GBM) (1). The immunopathogenic role of the anti-GBM antibodies has been established, and the target antigen (the Goodpasture antigen) has recently been identified as the non-collagenous domain of the α-3 chain of type IV collagen (2).

The incidence of Goodpasture’s syndrome is lower in Japan than in Western countries; only 13 reported cases in Japan have fulfilled the above three criteria of the syndrome. We report here an additional case of Goodpasture’s syndrome, and analyze clinical characteristics of the Japanese patients.

Case Report

A 75-yr-old man was admitted to Yuri-Kumiai General Hospital because of general fatigue and oliguria on December 28, 1989. He had been treated for angina pectoris since 1983 at the outpatient clinic, and had been well. In May 1988, a routine examination showed that the urine was normal, and that there was no abnormal level of blood urea nitrogen or serum creatinine. Since September 1988, he suffered from dry cough and shortness of breath. At that time, fine crackles were audible throughout both lungs. A blood gas analysis and respiratory function tests gave normal results. A mild form of interstitial pneumonitis was considered, although its etiology was uncertain. He was treated with a small dose of corticosteroids for 6 months, and his symptoms improved. In July 1989, he remained well, but a small nodular lesion (2 x 2 cm) was found in the S3 segment of the left lung on the follow-up radiological examination. Several weeks later, this lesion disappeared spontaneously. Since the middle of December 1989, he suffered from general fatigue, and noted oliguria a few days prior to admission.

On physical examination he was alert. The pulse was...
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72/min and regular, and the blood pressure was 140/90 mmHg. No rash or lymphadenopathy was found. The head and neck were normal. Crackles or rhonchi were not heard throughout either lung. The heart sounds were normal. Examination of the abdomen was negative except for a mild hepatomegaly. No peripheral edema, finger clubbing, or cyanosis was detected. Neurological examination was negative.

The urine volume was less than 300 ml/day, and both proteinuria (224 mg/dl) and hematuria were detected. Hemoglobin was 12.2 g/dl, white cell count, 6,700/μl, and platelet count, 250,000/μl. Blood urea nitrogen was 62.6 mg/dl, serum creatinine 18.1 mg/dl, uric acid 11.4 mg/dl, total bilirubin 0.4 mg/dl, aspartate aminotransferase 15 U/l, lactate dehydrogenase 358 U/l, and total cholesterol 168 mg/dl. Total protein was 6.2 g/dl (the albumin 3.2 g/dl and γ-globulin 2.5 g/dl). Serum sodium was 136 mEq/l, potassium 7.7 mEq/l, and chloride 105 mEq/l. The fractional excretion of sodium was 7%. Serum IgG was 2,680 mg/dl, IgA 617 mg/dl, and IgM 227 mg/dl. Serum C3 was 40.5 mg/dl, C4 36.0 mg/dl, and CH50 40.5 U/ml. Tests for antinuclear antibodies were negative, and cryoglobulin was not detected. An electrocardiogram revealed tall, tented T wave. An X-ray film of the chest disclosed a mild cardiomegaly and small pleural effusions. Bilateral lung fields appeared normal, and the abnormalities previously observed were not found. A specimen of arterial blood, drawn while the patient was breathing room air, showed that the partial pressure of oxygen (PaO₂) was 108 mmHg, the partial pressure of carbon dioxide (PaCO₂) 26 mmHg, bicarbonate 8.5 mmol/l, and pH 7.14. A computed tomographic scan of the abdomen revealed enlargement of both kidneys.

Based on these findings, acute renal failure due to rapidly progressive glomerulonephritis was considered, and daily hemodialysis was started on the first hospital day. On January 5, 1990, additional clinical manifestations consistent with pulmonary hemorrhage abruptly occurred, i.e., productive cough, bloody sputa, and dyspnea. Crackles and rhonchi were also audible throughout both lungs. Diffuse alveolar shadows appeared on an X-ray film of the chest. Goodpasture’s syndrome was considered, and he was treated with a bolus dose of methylprednisolone (1,000 mg/day, for 3 days) and plasma exchange (1,500 to 2,000 ml/day, for 3 days). However, on January 12 he died from respiratory failure due to massive pulmonary hemorrhage.

![Fig. 1. Autopsy findings. (A) Light microscopic appearance of the lung (HE stain, ×130). Marked intralveolar hemorrhage and thickening of the alveolar walls are observed. (B) Direct immunofluorescent staining of the lung, by using FITC-conjugated anti-human IgG (×160). Linear deposits of IgG conform to the distribution of partly disrupted alveolar walls. (C) Light microscopic appearance of the kidney (PAS stain, ×320). The glomerular tufts are compressed by extensive crescent formation. (D) Direct immunofluorescent staining of the kidney, by using FITC-conjugated anti-human IgG (×250). Linear deposits of IgG along the glomerular basement membrane are present.](image)
An autopsy was performed. The lungs showed marked intraalveolar hemorrhage (Fig. 1A). In addition, a thickening of the alveolar walls with linear deposits of IgG was observed (Fig. 1A and B). The kidneys were swollen. Almost all the glomeruli accompanied cellular or fibrous crescents, and the glomerular tufts were collapsed (Fig. 1C). Immunofluorescent studies revealed linear deposits of IgG along the GBM (Fig. 1D). The presence of circulating anti-GBM antibodies was confirmed by indirect immunofluorescent techniques (Fig. 2).

Discussion

We reported an autopsy case of Goodpasture's syndrome. This patient had a history of steroid-responsive interstitial pneumonitis and a transient pulmonary nodular lesion about 16 months before admission. These two findings seem to be related to the early clinical manifestations of Goodpasture's syndrome. About 5 months after the latter finding, the patient developed oliguric renal failure followed by life-threatening pulmonary hemorrhage. Intensive treatment with a bolus dose of methylprednisolone and plasma exchange was ineffective. This may be due to the advanced disease, as shown by autopsy findings, and the advanced age of the patient.

Anti-GBM antibody-induced glomerulonephritis is responsible for about 5% of glomerulonephritides in the West (3); about one- to two-thirds of the patients having this form of glomerulonephritis develop pulmonary hemorrhage, or Goodpasture's syndrome (3, 4). The term, "Goodpasture's syndrome" which was originally proposed by Stanton and Tange (5) in 1958 to describe cases of pulmonary hemorrhage associated with glomerulonephritis, is now used in a more restricted sense, referring only to those cases in which there is additional evidence of the presence of circulating anti-GBM antibodies (1). On the basis of the above criteria, Goodpasture's syndrome can be distinguished from other disorders with both pulmonary hemorrhage and glomerulonephritis, such as systemic lupus erythematosus, necrotizing vasculitis, Wegener's granulomatosis, and mixed cryoglobulinemia.

This syndrome is more common in the West than in the Orient, and the incidence of the syndrome is extremely low in Japan. The first Japanese case described as Goodpasture's syndrome was reported by Kinoshita et al (6) in 1964. According to a review by Ito et al (7), 13 cases were reported as Goodpasture's syndrome between 1964 to 1970 in Japan, but the diagnosis of those early reported cases was essentially based on circumstantial clinico-pathological findings. Gonda (8) reviewed additional 32 cases reported between 1974 to 1984 in Japan. Among these cases, however, only six cases fulfilled the three criteria for the diagnosis of Goodpasture's syndrome. Thereafter, additional seven definite cases have been reported in Japan.

The clinical features of the 13 Japanese patients previously reported (9–30) and the present case are summarized in Table 1. In marked contrast to the patients with Goodpasture's syndrome reported in the West (3, 4), who are usually young adult males, the majority of the Japanese patients are of middle or advanced age. Although the initial symptoms are varied, like the western patients, 13 out of 14 patients had a course which was rapidly progressive to renal failure requiring dialysis. Immunosuppressive treatment and plasma exchange were performed in 11 and 5 patients, respectively. These treatments were judged to be effective in 5 out of 6 living patients, but five patients died from respiratory failure or fungal infection as a side effect. Among three patients who received conservative treatment, two patients died from respiratory failure.

We also reviewed Japanese cases of anti-GBM antibody-induced glomerulonephritis without pulmonary hemorrhage. Only nine cases of this disease, in which there is evidence for the presence of circulating anti-GBM antibodies, have been reported in Japan (24, 25, 31–42) (Table 2). In a large series in the West reported by Savage et al (4), the majority of their patients were elderly women. On the other hand, most Japanese patients are males of middle or advanced age. All the patients developed progressive renal failure, and two early reported patients died from complications. Immuno-suppressive treatment and plasma exchange were performed in 5 and 2 patients, respectively. These treatments were effective in 4 patients, although the disease relapsed in 2 patients.

In summary, we reported the 14th confirmatory case of
Table 1. Clinical Profiles of Japanese Patients with Goodpasture’s Syndrome

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Initial symptoms (interval)*</th>
<th>Renal failure</th>
<th>Immunosuppression</th>
<th>Plasma exchange</th>
<th>Course</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26/β</td>
<td>lung (3 mo)</td>
<td>+</td>
<td>S</td>
<td></td>
<td>alive (on dialysis) (nephrectomized)</td>
<td>(9)<em>, (10)</em></td>
</tr>
<tr>
<td>2</td>
<td>28/β</td>
<td>lung (5 mo)</td>
<td>+</td>
<td>S</td>
<td></td>
<td>alive</td>
<td>(11)*</td>
</tr>
<tr>
<td>3</td>
<td>52/β</td>
<td>lung kidney</td>
<td>+</td>
<td>S</td>
<td></td>
<td>alive</td>
<td>(12)*</td>
</tr>
<tr>
<td>4</td>
<td>19/β</td>
<td>lung kidney</td>
<td>+</td>
<td>S</td>
<td></td>
<td>alive</td>
<td>(13)*</td>
</tr>
<tr>
<td>5</td>
<td>68/β</td>
<td>lung (6 mo)</td>
<td>+</td>
<td>S</td>
<td></td>
<td>alive</td>
<td>(14)*, (15)**</td>
</tr>
<tr>
<td>6</td>
<td>40/β</td>
<td>lung (1 mo)</td>
<td>+</td>
<td>SC</td>
<td></td>
<td>alive</td>
<td>(16)*, (17)**</td>
</tr>
<tr>
<td>7</td>
<td>56/β</td>
<td>kidney (2 wk)</td>
<td>+</td>
<td>S</td>
<td></td>
<td>died (respiratory failure)</td>
<td>(18)<em>, (19)</em>**, (20)</td>
</tr>
<tr>
<td>8</td>
<td>59/β</td>
<td>kidney (1 mo)</td>
<td>+</td>
<td>SA</td>
<td></td>
<td>died (fungal infection)</td>
<td>(21)*, (22)**</td>
</tr>
<tr>
<td>9</td>
<td>61/β</td>
<td>lung (? )</td>
<td>+</td>
<td>S</td>
<td></td>
<td>died (respiratory failure)</td>
<td>(23)<em>, (24)</em>, (25)**</td>
</tr>
<tr>
<td>10</td>
<td>41/β</td>
<td>kidney (3 mo)</td>
<td>+</td>
<td>SC</td>
<td></td>
<td>alive</td>
<td>(26)<em>, (27)</em>**</td>
</tr>
<tr>
<td>11</td>
<td>75/β</td>
<td>lung kidney</td>
<td>+</td>
<td>S</td>
<td></td>
<td>died (respiratory failure)</td>
<td>(28)*</td>
</tr>
<tr>
<td>12</td>
<td>29/β</td>
<td>lung kidney</td>
<td>+</td>
<td>S</td>
<td></td>
<td>died (sepsis)</td>
<td>(29)*</td>
</tr>
<tr>
<td>13</td>
<td>73/β</td>
<td>kidney (4 wk)</td>
<td>+</td>
<td>S</td>
<td></td>
<td>died (respiratory failure)</td>
<td>(30)*</td>
</tr>
<tr>
<td>14</td>
<td>75/β</td>
<td>lung (16 mo)</td>
<td>+</td>
<td>S</td>
<td></td>
<td>died (respiratory failure)</td>
<td>Present case</td>
</tr>
</tbody>
</table>

S, steroids; C, cyclophosphamide; A, azathioprine.

Goodpasture’s syndrome in Japan. A review of the Japanese cases of Goodpasture’s syndrome or of anti-GBM antibody-induced glomerulonephritis reveals that the majority of the Japanese patients with these disorders are males of middle or advanced age. On the other hand, for unknown reasons, two distinct patterns have been recognized in the western patients with anti-GBM antibody-induced glomerulonephritis: young adult males with Goodpasture’s syndrome and elderly women with glomerulonephritis alone (4). The number of reported cases of anti-GBM antibody-induced glomerulonephritis has recently been increasing in Japan. Wider application of sensitive assays for circulating anti-GBM antibodies like those used in the West (4) would provide further information concerning the clinical characteristics of Japanese patients.

References
Table 2. Clinical Profiles of Japanese Patients with Anti-glomerular Basement Membrane Antibody-induced Glomerulonephritis without Pulmonary Hemorrhage

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Renal failure</th>
<th>Immuno-suppression</th>
<th>Plasma exchange</th>
<th>Course</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86/♂</td>
<td>+</td>
<td></td>
<td></td>
<td>died</td>
<td>(31)*, (32)**</td>
</tr>
<tr>
<td>2</td>
<td>48/♀</td>
<td>+</td>
<td></td>
<td></td>
<td>died</td>
<td>(33)*</td>
</tr>
<tr>
<td>3</td>
<td>67/♂</td>
<td>+</td>
<td></td>
<td></td>
<td>alive</td>
<td>(34)*</td>
</tr>
<tr>
<td>4</td>
<td>54/♂</td>
<td>+</td>
<td></td>
<td></td>
<td>alive</td>
<td>(35)*</td>
</tr>
<tr>
<td>5</td>
<td>56/♂</td>
<td>+</td>
<td></td>
<td></td>
<td>alive</td>
<td>(36)*</td>
</tr>
<tr>
<td>6</td>
<td>69/♂</td>
<td>+</td>
<td></td>
<td></td>
<td>alive</td>
<td>(24)*, (25)**</td>
</tr>
<tr>
<td>7</td>
<td>53/♂</td>
<td>+</td>
<td></td>
<td></td>
<td>alive</td>
<td>(37)<em>, (38)</em>, (39)</td>
</tr>
<tr>
<td>8</td>
<td>28/♂</td>
<td>+</td>
<td></td>
<td></td>
<td>alive</td>
<td>(40)*, (41)**</td>
</tr>
<tr>
<td>9</td>
<td>69/♂</td>
<td>+</td>
<td></td>
<td></td>
<td>alive</td>
<td>(42)*</td>
</tr>
</tbody>
</table>

* Japanese abstract, ** in Japanese with an English abstract.
S, steroids; NA, not available.

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