A Case of Anti-Glomerular Basement Membrane Antibody-Positive Systemic Lupus Erythematosus with Pulmonary Hemorrhage Successfully Treated at an Early Stage of the Disease

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We report here a case of systemic lupus erythematosus (SLE) with pulmonary hemorrhage and anti-glomerular basement membrane (anti-GBM) antibodies. A 42-year-old woman was admitted to our hospital with complaints of exanthema, arthralgia, shortness of breath, and hemoptysis. Plain chest computed tomography (CT) scan revealed pericardial effusion, bilateral pleural effusions, and pulmonary hemorrhage. Laboratory findings on admission revealed proteinuria, microscopic hematuria, anemia, leukopenia, hypoalbuminemia, hypocomplementemia, and slightly elevated levels of serum creatinine. Serological tests revealed elevated titers of serum anti-GBM antibodies, proteinase 3-antineutrophil cytoplasmic antibodies (PR3-ANCA), and anti-double stranded deoxyribonucleic acid (dsDNA)-immunoglobulin G (IgG) antibodies. Early treatment with steroid pulse therapy combined with plasma exchange resolved the patient’s pulmonary hemorrhage and renal dysfunction. Renal biopsy carried out after the treatment revealed a recovery phase of acute tubular injury with minor glomerular abnormalities without linear IgG deposition along the GBMs. For a good prognosis, it is necessary to start treatment immediately in patients with anti-GBM antibody-positive SLE associated with pulmonary hemorrhage. (J Nippon Med Sch 2018; 85: 138-144)

Key words: SLE, anti-GBM antibodies, pulmonary hemorrhage

Introduction

Anti-glomerular basement membrane (anti-GBM) disease is defined by the presence of autoantibodies that bind to the α3 chain of type IV collagen in pulmonary and glomerular basement membranes. The term “Goodpasture’s syndrome” (GPS) is used for patients with both pulmonary hemorrhage and glomerulonephritis caused by anti-GBM antibodies1-3. Anti-GBM disease encompasses any disease caused by anti-GBM antibodies, which includes not only GPS but also isolated anti-GBM glomerulonephritis without pulmonary hemorrhage and isolated anti-GBM pulmonary hemorrhage without glomerulonephritis4,5.

Recently, case reports of atypical GPS with normal renal function have increased6,7. Although the renal function of the patients suffering from this condition was normal, renal biopsy specimens revealed a characteristic linear IgG deposition along the GBMs.

Systemic lupus erythematosus (SLE) is sometimes accompanied by pulmonary hemorrhage. Although SLE associated with anti-GBM antibodies is rare, Yamazaki et al.8 and Nakamura et al.9 reported elevated titers of anti-GBM antibodies at the onset of pulmonary hemorrhage in cases of SLE.

Recently, we have encountered a case of SLE associated with pulmonary hemorrhage. Pathological features of renal biopsy specimens helped us to differentiate the present case from GPS with normal renal function.
Table 1 Laboratory findings on admission (a). Titters of anti-GBM-antibodies, PR3-ANCA, anti-dsDNA-IgG antibodies and anti-cardiolipin IgG antibodies before and after treatment (b).

<table>
<thead>
<tr>
<th>Table 1a</th>
<th>Table 1b</th>
<th>before</th>
<th>after</th>
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<td>Urinalysis</td>
<td>BC</td>
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<td>T.Bil</td>
<td>LDL-chol</td>
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<td>Glu. (-)</td>
<td>AST</td>
<td>Serology)</td>
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<tr>
<td>Urobili. (+/-)</td>
<td>ALT</td>
<td>CRP</td>
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<td>Bil. (-)</td>
<td>g-GTP</td>
<td>IgG</td>
<td>1.265 mg/dL</td>
</tr>
<tr>
<td>Ket. (-)</td>
<td>ALP</td>
<td>IgA</td>
<td>146 mg/dL</td>
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<td>IgM</td>
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<tr>
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<td>TP</td>
<td>CH50</td>
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<tr>
<td>RBC 50+/HPF</td>
<td>Alb</td>
<td>C3</td>
<td>78 mg/dL</td>
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<tr>
<td>WBC 5-9/HPF</td>
<td>CK</td>
<td>C4</td>
<td>12 mg/dL</td>
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<tr>
<td>Casts 50-99/HPF</td>
<td>Amy</td>
<td>anti-nuclear-Ab</td>
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<tr>
<td>CBC</td>
<td>BUN</td>
<td>anti-dsDNAIgG</td>
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<tr>
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<td>Cr</td>
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<td>Hct</td>
<td>Cl</td>
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<tr>
<td>MCV</td>
<td>Ca</td>
<td>RPR</td>
<td>(2)</td>
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<tr>
<td>MCH</td>
<td>P</td>
<td>TPLA</td>
<td>(-)</td>
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<tr>
<td>MCHC</td>
<td>Glu</td>
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<tr>
<td>PLT</td>
<td>T.chol</td>
<td>Urinary β2-MG</td>
<td>386 mg/L</td>
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Case Report

A 42-year-old female patient was admitted to our hospital with complaints of exanthema, arthralgia, shortness of breath, and hemoptysis. These symptoms began 10 days before her admission and progressively worsened. Laboratory findings on admission revealed proteinuria, microscopic hematuria, hypoalbuminemia, hypocomplementemia, anemia, leukopenia, and slightly elevated levels of serum creatinine. Her serological tests revealed elevated titers of anti-nuclear antibodies (ANA), anti-dsDNA-IgG antibodies, and anti-cardiolipin IgG antibodies. Her rapid plasma regain card agglutination test was positive, whereas her Treponema pallidum latex agglutination test was negative (Table 1a). A plain chest radiography and CT scan taken on admission revealed a pericardial effusion, bilateral pleural effusions, and a frosted glassy shadow on both lung fields, indicating alveolar infiltration (Fig. 1a, 1b, 1e). Her ejection fraction estimated by ultrasonic echocardiography on admission was 63.5%, indicating normal cardiac function. On the 4th day of hospitalization, alveolar infiltration increased, and new findings of pulmonary hemorrhage appeared on her chest CT (Fig. 1c). Furthermore, the titers of anti-GBM antibodies as well as PR3-ANCA on admission were elevated (Table 1a). At first, she was diagnosed with anti-GBM antibody disease associated with SLE and treated with a steroid pulse (a bolus dose of methylprednisolone; 1 g/day, for 3 days) followed by oral administration of prednisolone (40 mg/day) and plasma exchange (frozen fresh plasma; 2,000 mL/day, for 5 days). Pulmonary hemorrhage and infiltration disappeared on the CT scan taken on the 14th day of hospitalization (Fig. 1d, 1g). Proteinuria also disappeared, and serum creatinine levels returned to normal. She was relieved of the symptoms that were observed on admission. Anti-GBM antibody titers and PR3-ANCA became negative on the 12th day of hospitalization (Table 1b). A percutaneous renal biopsy was undertaken on the 19th day of hospitalization and revealed minor glomerular abnormalities (Fig. 2a), with 2 of the 16 glomeruli showing slight capillary wrinkling and retardation (Fig. 2b), tubulointerstitial monocyte infiltration, and flattening of tubular epithelial cells, indicating the recovery phase of acute tubular injury (Fig. 3). On immunofluorescence, granular depositions of IgM, IgG, IgA, and C3 were seen in the mesangial region without linear IgG deposition along the GBMs (Fig. 4). Electron microscopy (EM) revealed no electron-dense deposits in the glomeruli (Fig. 5). These pathological features made us...
Fig. 1 Chest X-ray on admission revealed a ground glass opacity in both lung fields (a). Chest computed tomography (CT) scan in the pulmonary window on admission (b), the 4th day of hospitalization (c), and the 14th day of hospitalization (d). Chest CT scan in the mediastinal window on admission (e), the 4th day of hospitalization (f), and the 14th day of hospitalization (g).

Fig. 2 Pathological findings of the renal biopsy. Light microscopy revealed minor glomerular abnormalities in the cortical region (a, HE stains, 400×). Slight capillary wrinkling and retardation are seen in 2 of the 16 glomeruli (b, PAM stains, 400×).

change the first diagnosis of anti-GBM antibody disease with SLE to anti-GBM antibody-positive SLE because of the absence of the characteristic linear IgG deposition along the GBMs. The patient was discharged on the 53rd day of hospitalization without renal dysfunction and continued to receive outpatient treatment.

Discussion
In this report, we presented a case of anti-GBM antibody-positive SLE successfully treated with methylprednisolone pulse therapy and plasma exchange, preventing the patient from developing renal impairment. The patient was relieved of the symptoms recognized on admission, including decreased pulmonary hemorrhage, and anti-GBM antibody became negative after the treatment.

Recently, case reports of atypical GPS with normal renal function have increased significantly. The prognosis of these cases has been reported to be good. Although these cases were atypical as they presented with normal renal function, they were accompanied by a typical linear IgG deposition along the GBMs. On the contrary, linear IgG deposition on the GBMs was not observed in the present case, although laboratory findings on admission revealed positive anti-GBM antibodies. Moreover, the
Anti-GBM antibody positive SLE

HE (x200)

Fig. 3 Pathological findings of the renal biopsy. Light microscopy revealed flattened epithelial cells, dilated tubular lumens, and infiltrated monocytes in the tubulointerstitial region (HE stains, 200×).

Fig. 4 Immunofluorescence studies revealed granular depositions of IgM, IgG, IgA, and C3 without linear IgG deposition along the GBMs in the glomeruli.

The present case revealed slight capillary wrinkling and retardation and a recovery phase of acute tubular injury, which was not described in previous reports. At first, we speculated that the absence of IgG deposits
There are no electron-dense deposits in the glomeruli. Along the GBMs in the present case was due to the disappearance of those deposits as a renal biopsy was carried out on the 19th day of hospitalization when the patient had already made a remarkable recovery. Lamriben et al. reported the disappearance of anti-GBM antibody deposits after treatment. In the present case, the patient’s condition was too critical to undergo a renal biopsy in the acute phase of the disease. Thus, we could not clarify the pathological features, including IgG deposition, during the critical phase of the disease.

Afterward, however, EM revealed that there were no electron-dense deposits in the glomeruli (Fig. 5). The possibility that IgG deposition had disappeared after the treatment became quite low. Therefore, we concluded that the present case did not involve atypical GPS with normal renal function as previously reported elsewhere. The present case revealed some typical features of SLE. Arthralgia and exanthema were the chief complaints on admission. Laboratory findings on admission revealed leukopenia, anemia, hypocomplementemia, and a mildly elevated serum creatinine level; serological tests revealed mildly elevated titers of ANA, anti-dsDNA-IgG antibodies, and anti-cardiolipin IgG antibodies and a falsely positive result for syphilis was given. Proteinuria and microscopic hematuria were seen on urinary analysis (Table 1a). A plain chest CT scan revealed pleural and pericardial effusions (Fig. 1b, 1e). Taken together, the present case fulfilled at least 4 of the Systemic Lupus International Collaborating Clinics classification criteria for SLE.

Furthermore, serological tests revealed minor elevated titers of anti-GBM antibodies and PR3-ANCA (Table 1a). Patients who have SLE with renal and pulmonary involvement can have anti-GBM antibody disease or ANCA-associated vasculitis. However, serum complement levels are typically normal or elevated in anti-GBM disease and ANCA-associated vasculitis, unlike in the present case. Therefore, we diagnosed the present patient with SLE with an increase in anti-GBM antibody titer at the onset of pulmonary hemorrhage.

Recently, synchronized increases in serum anti-GBM antibodies and pulmonary hemorrhage in patients with SLE have been reported. Yamazaki et al. and Nakamura et al. reported rare cases of SLE associated with an increase in anti-GBM antibody titers. In their reports, an elevated titer of anti-GBM antibodies was accompanied by pulmonary hemorrhage in patients with SLE and severe renal dysfunction or lupus nephritis. The relationship between SLE and anti-GBM antibodies is less well known. Yamazaki et al. formulated the hypothesis that the basement membrane of the lung or kidney were damaged first by interstitial pneumonitis due to SLE or lupus nephritis, leading to exposure of the basement antigens and the subsequent production of anti-GBM antibodies.

Although elevated titers of anti-GBM antibodies, anti-dsDNA-IgG antibodies, and serum creatinine were slight in the present case, the clinical manifestation of pulmonary hemorrhage was critical. The titers of both anti-GBM and anti-dsDNA-IgG antibodies decreased simultaneously to normal levels after treatment (Table 1b). Pulmonary hemorrhage can be a fatal complication in the early phase of the onset of SLE. One possibility is that our treatments were completed before the patient developed severe renal impairment. We evaluated that the lack of overt glomerulonephritis was due to the early detection and treatment of pulmonary hemorrhage. Thus, we diagnosed the present patient with an early phase of anti-GBM antibody-positive SLE followed with an onset of pulmonary hemorrhage.

Histological findings of specimens obtained from renal biopsy revealed a recovery phase of acute ischemic injury of the tubulointerstitial region and minor glomerular abnormalities (Fig. 2, 3). We speculated that the pulmonary hemorrhage induced an intravascular dehydration. Pathological features that resemble acute tubular necrosis may occur as a result of impaired perfusion of the peritubular capillaries due to pulmonary hemorrhage. In fact, the present case revealed severe anemia on admission and elevated urinary levels of β2-microglobulin (Table 1).
a). In the present case, mesangial deposits of immune complexes were not seen, indicating that this patient did not present signs of lupus nephritis, according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis20.

To the best of our knowledge, this is the first case report to reveal that pulmonary hemorrhage could occur even with slightly elevated titers of anti-GBM- and anti-dsDNA-IgG antibodies and minor glomerular abnormalities. Treatment with plasma exchange and methylprednisolone pulse therapy at an early stage of the disease diminished the massive pulmonary hemorrhage. Simultaneous increases and decreases in anti-GBM- and anti-dsDNA-IgG antibodies were noted before and after the treatment, respectively.

PR3-ANCA was also positive on admission. Kaliuri et al.21 reported an unusual association of PR3-ANCA and anti-GBM antibody disease. Little is known about the clinical significance of the coexistence of anti-GBM antibodies and PR3-ANCA, even though combinations of anti-GBM antibodies and myeloperoxidase-ANCA have been reported to have an influence on prognosis22,23.

Finally, we have successfully treated a case of anti-GBM antibody-positive SLE with methylprednisolone pulse therapy and plasma exchange at an early stage of the disease. Slightly elevated titers of anti-GBM and anti-dsDNA-IgG antibodies were seen with pulmonary hemorrhage. These 2 antibodies decreased to normal levels synchronously after the treatment. Renal biopsy specimens revealed almost intact glomeruli and ischemic damage of tubules. The present case highlights that physicians need to be aware of the sudden onset of pulmonary hemorrhage even with mildly elevated titers of anti-GBM- and anti-dsDNA-IgG antibodies. Early initiation of treatment is required for a good prognosis.

Conflict of Interest: The authors declare no conflict interest.

References


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