Pulmonary-Limited Granulomatosis with Polyangiitis Coexisting with Mixed Connective Tissue Disease

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Granulomatosis with polyangiitis (GPA) is a systemic disease characterized by necrotizing, granulomatous vasculitis of the upper and lower respiratory tracts and glomerulonephritis, and is classified as a classical or limited form. The classical form of GPA demonstrates the involvement of the upper respiratory tract, sinuses, lungs and kidneys, whereas the limited form is characterized by the lack of the renal involvement with female predominance. On the other hand, mixed connective tissue disease (MCTD) shows the clinical and laboratory features of systemic lupus erythematosus, systemic sclerosis and polymyositis, along with high titers of anti-ribonucleoprotein antibodies and is characterized by good response to corticosteroid therapy and favorable prognosis. We herein report a patient with a history of MCTD that developed into a limited form of GPA (pulmonary-limited GPA). A 39-year-old woman suffered from persistent cough, left back pain and appetite loss. At 21 years of age she was diagnosed with MCTD, but the persistent administration of prednisolone or immunosuppressants was not needed. On admission, high-resolution chest computed tomography showed bilateral, multiple, poorly circumscribed nodules and masses, some of which showed cavitation. A surgical lung biopsy demonstrated granulomas with vasculitis surrounding the necrotic lesions. She was diagnosed with pulmonary-limited GPA. In conclusion, we should recognize that GPA may develop during the disease course of MCTD even after prolonged disease remission. To prevent progression to an irreversible state, physicians should consider a surgical lung biopsy for the diagnosis in patients suspected of having pulmonary-limited GPA.

Keywords: anti-neutrophil cytoplasmic antibody-associated vasculitis; granulomatosis with polyangiitis; human leukocyte antigen genotype; mixed connective tissue disease; shared autoimmunity

Received March 9, 2017; revised and accepted May 22, 2017. Published online June 7, 2017; doi: 10.1620/tjem.242.109.
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ANCA) and proteinase 3-ANCA (PR3-ANCA) were not analyzed, and she had no clinical manifestations of GPA. Chest computed tomography revealed pleural effusion without any pulmonary parenchymal abnormalities. She met the criteria of The Research Committee of the Japanese Ministry of Health and Welfare for MCTD. Prednisolone (30 mg/day) was administered, and the initial dose was subsequently tapered. Steroid treatment was stopped at six weeks. Afterwards, she was transiently prescribed oral prednisolone (PSL) when she suffered from arthralgia. At 33 years of age, she was diagnosed with hypothyroidism, which was treated with Levothyroxine. She was a never smoker.

A physical examination revealed that her body temperature was 37.1°C while a pulse oximetry revealed 97% oxygen saturation on room air. A physical examination revealed no vision disturbance, a narrow visual field and saddle nose. Auscultation revealed normal vesicular breath sounds. There were no neurological abnormalities or skin lesions. Oxygen desaturation was observed during a 6-min walk test (lowest oxygen saturation: 89%).

A complete blood count (CBC) revealed the following findings: RBC count, $417 \times 10^4/\mu L$ (normal range: 386-492 $\times 10^4/\mu L$); hemoglobin, 12.0 mg/dl (normal range: 11.6-14.8 mg/dl); and WBC count, 6,400/μL (normal range: 3,300-8,600/μL).

A blood chemistry analysis revealed the following findings: BUN, 7.4 mg/dl (normal range: 8-20 mg/dl); Creatinine, 0.6 mg/dl (normal range: 0.46-0.79 mg/dl); and CRP, 1.00 mg/dl (normal range: 0-0.14 mg/dl). An assay of antinuclear antibody and anti-RNP antibody showed titers of 1,280 (normal range: < 10) and 4,256 U/ml (normal range: < 10 U/ml). The patient was positive for both MPO-ANCA and PR3-ANCA, at titers of 38.9 U/ml (normal: < 9 U/ml), 27.1 U/ml (normal: < 3.5 U/ml), respectively. A urinary test showed no abnormal findings.

A chest X-ray revealed faint infiltrations with cavitation in the lower right field (Fig. 1a). High-resolution chest computed tomography showed bilateral, multiple, poorly circumscribed nodules and masses (Fig. 1b). Some of them showed cavitations. A pulmonary function test revealed a restrictive pattern (vital capacity [VC], 2.33L; VC percent predicted [%VC], 77.2%; forced expiratory volume in one second [FEV1], 2.09L; and the FEV1/forced VC ratio [FEV1%], 86%) while the diffusing capacity of the lungs for carbon monoxide (DLco) level was within the normal limits (14.08 mL/min/mmHg; %DLco 82.5%). After a transbronchial biopsy failed to confirm the diagnosis, a video assisted surgical lung biopsy was performed. The histological examination of the left lower lung nodule revealed arteritis with neutrophil infiltration. Granulomas with multinucleated giant cells were found surrounding the necrotic lesions (Fig. 2). Based on the biopsy and the serological findings, she was diagnosed with pulmonary-limited GPA, which presented as multiple lung nodules.

Pulsed methylprednisolone therapy (0.5 g/day for 3 days) was administered followed by the prednisolone (35 mg/day, orally). The dose of prednisolone was tapered to 10 mg. After 6 months of immunosuppressive therapy, the CT findings were ameliorated (Fig. 1c) and a lung function test revealed that the patient’s %VC had improved from 77.2% to 88.3%.

**Discussion**

GPA is a multi-systemic disorder with distinct clinical patterns. The features consist of necrotizing granuloma and vasculitis of the upper and lower respiratory tracts, varied degrees of small vessel vasculitis and focal necrotizing glomerulonephritis. In 1966, Carrington and Liebow (1966) described 16 patients with pulmonary lesions identical to those of Wegener’s Granulomatosis (WG) with the absence of focal glomerulitis. The character-
istics of patients with limited WG have been reported to include a female predominance, younger age and a lower frequency of PR3-ANCA or MPO-ANCA positivity in comparison to those with the severe form (Stone 2003). It has a high propensity for relapse following periods of remission (Stone 2003; Hogan et al. 2005), and can cause significant local damage such as saddle nose deformity over time (Martinez Del Pero et al. 2011). The pulmonary findings in limited WG are similar to those of the classical form, in which multiple and bilateral lesions are found in two-thirds of cases and cavitating lesions are found in one-third of cases (Carrington and Liebow 1966).

Under the criteria of the American College of Rheumatology, GPA is defined by the presence of at least two of the following four criteria: sinus involvement; lung X-ray showing nodules, a fixed pulmonary infiltrate or cavitities; urinary sediment with hematuria or red cell casts; and histological granulomas within an artery or in the perivascular area of an artery or arteriole (Leavitt et al. 1990). Thus, in order to confirm a diagnosis of a pulmonary-limited GPA, the histopathological findings of lung specimens must be evaluated. GPA can be fatal if left untreated (Kaneishi et al. 1995). An early diagnosis and treatment can prevent renal failure, which is the most common cause of death (Mark et al. 1988). As trans-bronchial biopsies (TBLBs) of alveolar tissue are seldom positive in GPA with mild-to-moderate pulmonary involvement, unless they are taken from grossly abnormal lung areas, a surgical lung biopsy is necessary to confirm the diagnosis.

Recently, Tubery et al. (2016) reported for the first time a case of MCTD who secondarily developed severe GPA. A retrospective multicenter study of a laboratory databases in 10 European centers revealed 18 cases of anti-RNP and anti-PR3-ANCA double positivity in 11,921 samples, and only 1 case (reported case) showed both MCTD and GPA symptoms (Tubery et al. 2016). This study revealed that the coexistence of anti-RNP and anti-PR3-ANCA antibodies is very rare. To our knowledge, our case is the first of MCTD developing into pulmonary-limited GPA.

A search of the PubMed database revealed 10 reports of MCTD complicated with ANCA-associated vasculitis. The clinical features of these 10 cases and our own case are shown in Table 1 (Makita et al. 2000; Kanazawa et al. 2004; Hernandez-Molina et al. 2006; Kitaura et al. 2006; Murakami et al. 2011; Konstandinov et al. 2013; Murakami et al. 2013; Sun et al. 2014; Sato et al. 2016; Tubery et al. 2016). The 81.8 percent of the patients were female. The age at the diagnosis of ANCA-associated vasculitis ranged from 35 to 68 (median 48) years. MCTD and ANCA-associated vasculitis occurred simultaneously in three cases (27.2%) and seven patients (72.8%) with MCTD subsequently developed ANCA-associated vasculitis (duration; 3-28 years). Ten patients (90.9%) were positive for MPO-ANCA, and 4 (36.4%) were positive for PR3-ANCA, 3 (27.3%) patients were positive for both.

Most biopsies of affected lesions are obtained by a renal needle biopsy (63.6%); the present case is the first where the histopathological findings obtained by a surgical lung biopsy were crucial for making an accurate diagnosis. According to treatment, all patients received corticosteroids and seven patients (63.6%) received immunosuppressants. In admission, two patients (18.2%) received intravenous immunoglobulin therapy (IVIG). Two patients (18.2%) died due to sepsis and alveolar hemorrhage during the disease course.

As shown in Table 1, 9 of 12 cases (81.8%) were Asian and 10 cases (90.9%) demonstrated MPO-ANCA positivity. The high incidence of MPO-ANCA-related vasculitis in East Asia is assumed to be linked to Human Leukocyte Antigen (HLA) haplotypes, particularly HLA-DRB1*09:01, one of the most common HLA-DRB1 alleles in Asians but rare in Caucasian populations (Tsuchiya 2013). In contrast, the frequencies of HLA-DRB1*04:01, HLA-DRB4*01:01, HLA-DQA1*03 were significantly increased in patients with MCTD (Dong et al. 1993). Interestingly, our patient’s HLA genotype is HLA-DRB1*09:01 as well. However, Tubery et al. (2016)
reported a case of MCTD who secondarily developed severe GPA and whose HLA haplotype was not DRB1*09:01 but DRB1*04:12. In a German cohort with ANCA-associated systemic vasculitis, HLA-DRB1*4 individuals were over-represented among GPA patients with end-stage renal disease (Gencik et al. 1999). Although the HLA-DRB1*09:01 genotype may contribute to the development GPA in the disease course of MCTD, further studies are required to clarify the role of the HLA genotype in the pathogenesis of MCTD consecutively developing GPA.

The concurrence of 2 or more autoimmune disorder in the same individual has been described in patients with rheumatic connective tissue diseases, autoimmune-related thyroid diseases and inflammatory bowel diseases, and other conditions (Mackay 2009). These associations have been attributed to shared autoimmunity (Alarcon-Segovia et al. 2005). Patients who have one autoimmune disease may be more susceptible to developing a second and/or third disease, with the second and/or third disease appearing while the first disease is still active - even when adequate treatment is provided (Rodriguez-Reyna and Alarcon-Segovia 2006). In the present case, oral PSL was transiently required at the onset of MCTD, when the patient experienced arthralgia; thereafter, it was not prescribed for a number of years. At the onset of GPA, the serum anti-RNP antigen level was high, despite the prolonged remission of MCTD. As the referenced case reports in Table 1 demonstrated, 8 of 11 cases (72.7%) developed ANCA positivity of MCTD. As the referenced case reports in Table 1 demonstrated, 8 of 11 cases (72.7%) developed ANCA positivity after being diagnosed with MCTD. Interestingly, at the diagnosis of ANCA-associated vasculitis, these cases were in remission or in an inactive disease phase of MCTD; however, the serum titer of anti-RNP antibody remained high in all cases. It is controversial whether these cases are consistent with the concept of “shared autoimmunity”.

Although MCTD was characterized by overlapping features of SLE, SSC and PM, to our knowledge, cases of SLE coexistent with GPA are extremely rare (D’Cruz et al. 1993; Erdogan et al. 2004; Fukui et al. 2015) and there have been no case reports about SSC and PM coexistent with GPA. Erdogan et al. (2004) reported a pediatric case of SLE consecutively developing GPA and speculated that a viral infection might have been the triggering factor for the expression of ANCA target antigens leading to the development of GPA after the improvement of SLE with immunosuppressive therapy.

Table 1. The characteristics of the patients diagnosed with MCTD complicated with ANCA-associated vasculitis.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Sequence</th>
<th>Duration</th>
<th>ANCA positivity</th>
<th>Pathological finding</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Report</th>
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<tr>
<td>F</td>
<td>42</td>
<td>Simultaneous</td>
<td>3yr</td>
<td>MPO</td>
<td>Renal biopsy</td>
<td>GPA</td>
<td>PSL, CYP</td>
<td>Improve</td>
<td>Sun Y, 2014</td>
</tr>
<tr>
<td>M</td>
<td>64</td>
<td>Simultaneous</td>
<td>0</td>
<td>MPO</td>
<td>Renal biopsy</td>
<td>MPA</td>
<td>PSL, CYC</td>
<td>Improve</td>
<td>Sato S, 2016</td>
</tr>
<tr>
<td>F</td>
<td>38</td>
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<td>0</td>
<td>MPO / PR3</td>
<td>Fibrocellular crescents GN</td>
<td>AAGN</td>
<td>PSL, AZP</td>
<td>Improve</td>
<td>Murakami M, 2013</td>
</tr>
<tr>
<td>F</td>
<td>68</td>
<td>Simultaneous</td>
<td>4yr</td>
<td>MPO</td>
<td>Renal biopsy</td>
<td>AAGN</td>
<td>PSL</td>
<td>Dead due to sepsis</td>
<td>Murakami T, 2011</td>
</tr>
<tr>
<td>F</td>
<td>42</td>
<td>Simultaneous</td>
<td>6yr</td>
<td>MPO</td>
<td>Autopsy</td>
<td>MPA</td>
<td>PSL, IVCY Plasmapheresis</td>
<td>Dead due to alveolar hemorrhage</td>
<td>Kitaura K, 2006</td>
</tr>
<tr>
<td>F</td>
<td>47</td>
<td>Simultaneous</td>
<td>28yr</td>
<td>MPO</td>
<td>Renal biopsy</td>
<td>AAGN</td>
<td>PSL, IVCY</td>
<td>Improve</td>
<td>Hernandez-Molina G, 2006</td>
</tr>
<tr>
<td>F</td>
<td>47</td>
<td>Simultaneous</td>
<td>0</td>
<td>PR3</td>
<td>Renal biopsy</td>
<td>AAGN</td>
<td>PSL</td>
<td>Improve</td>
<td>Kanazawa M, 2004</td>
</tr>
<tr>
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<td>16yr</td>
<td>MPO</td>
<td>Renal biopsy</td>
<td>AAGN</td>
<td>PSL, IVIG</td>
<td>Improve</td>
<td>Makita N, 2000</td>
</tr>
<tr>
<td>F</td>
<td>39</td>
<td>Simultaneous</td>
<td>20 yr</td>
<td>MPO/PR3</td>
<td>Surgical lung biopsy</td>
<td>GPA</td>
<td>PSL</td>
<td>Improve</td>
<td>Present case</td>
</tr>
</tbody>
</table>

MCTD, mixed connective tissue disease; MPO, myeloperoxidase antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase-33 antineutrophil cytoplasmic antibody; GN, glomerulonephritis; GPA, granulomatous polyangiitis; MPA, microscopic polyangiitis; AAV, ANCA associated vasculitis; AAGN, ANCA associated glomerulonephritis; PSL, prednisolone; CYP, cyclophosphamide; CsA, cyclosporine; AZP, azathioprine; IVCY, intravenous cyclophosphamide.
In conclusion, this is the first reported case of primary-limited GPA coexisting with MCTD. We should recognize that GPA may develop during the disease course of MCTD even after prolonged disease remission. As an early diagnosis and appropriate treatment are important for preventing the progression of this disease to an irreversible state, physicians should consider a surgical lung biopsy for the diagnosis in patients suspected of having pulmonary-limited GPA.

Acknowledgments

We thank Prof. Kenji Sugio, Dr. Michiyo Miyawaki and Dr. Takafumi Hashimoto Department of Thoracic and Breast Surgery, Faculty of Medicine, Oita University for performing the lung biopsy by video assisted thoracoscopic surgery. We also thank Dr. Tsutomu Daa of the Department of Diagnostic Pathology, Faculty of Medicine, Oita University for the valuable assistance in obtaining the pulmonary histopathological records.

Conflict of Interest

The authors declare no conflict of interest.

References


