

Successful Immunosuppressive Treatment of Mixed Connective Tissue Disease Complicated by Microscopic Polyangiitis

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Mixed connective tissue disease (MCTD) is characterized by a combination of clinical features of systemic lupus erythematosus, systemic sclerosis, and polymyositis with elevated antibodies to U1 small nuclear ribonucleoprotein (U1-RNP). MCTD is often accompanied by interstitial lung disease as pulmonary involvement. On the other hand, microscopic polyangiitis (MPA) is a systemic autoimmune disease characterized by the inflammation of small vessels (arterioles, capillaries, and venules) mainly affecting the lung and kidney. MPA is associated with elevated serum anti-neutrophil cytoplasmic antibody (ANCA). Complication of MPA in patients with MCTD is rare. So far, only nine case reports of MCTD complicated by MPA with serum myeloperoxidase-specific ANCA (MPO-ANCA) are available. Here, we describe a 64-year-old male suffering from MCTD with MPA. The patient developed interstitial pneumonia with alveolar hemorrhage accompanied by myositis, scleroderma, and elevated anti-U1-RNP antibody and MPO-ANCA levels with substantial systemic inflammation. Strong immunosuppressive therapy (corticosteroid, intravenous immunoglobulin, and cyclosporine A) ameliorated the myositis, interstitial lung disease, and inflammation, with the decrease of MPO-ANCA levels, despite that severe lung complications are often associated with poor outcomes. In conclusion, MCTD may be accompanied by MPA with alveolar hemorrhage. Severe lung complications may indicate a poor outcome, and therefore prompt immunosuppressive treatment should be performed in such patients.

Keywords: alveolar hemorrhage; interstitial pneumonia; microscopic polyangiitis; mixed connective tissue disease; myeloperoxidase-specific anti-neutrophil cytoplasmic antibody

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Introduction

Mixed connective tissue disease (MCTD) is an overlap syndrome characterized by elevated anti-U1 small nuclear ribonucleoprotein (U1-RNP) antibodies, with the clinical features of systemic lupus erythematosus, systemic sclerosis (SSc), and polymyositis (Kasukawa 1999). MCTD is often accompanied by interstitial lung disease (30%) as pulmonary involvement (Horiki et al. 1998). However, alveolar hemorrhage is an extremely rare complication and may cause a fatal outcome (Germain and Davidman 1984; Horiki et al. 1998). Myeloperoxidase-specific anti-neutrophil cytoplasmic antibody (MPO-ANCA) positive polyangiitis (microscopic polyangiitis, MPA) is a systemic autoimmune disorder, which is characterized by the inflammation of small vessels (arterioles, capillaries, and venules) mainly affecting the lung and kidney (Murakami et al. 2011). Complication of MPA in patients with MCTD is rare. So

far, only nine MCTD cases accompanied by MPO-ANCA-positive MPA have been described (Inada et al. 1999; Makita et al. 2000; Hernández-Molina et al. 2006; Kitaura et al. 2006; Hong et al. 2010; Murakami et al. 2011; Konstantinov et al. 2013; Murakami et al. 2013; Sun et al. 2014). Here we report a rare case of MCTD complicated by MPA with alveolar hemorrhage, responding well to immunosuppressive treatment.

Case Presentation

A 64-year-old man was admitted to our hospital in February 2014. Since autumn 2013, he had been suffering from myalgia, numbness of the fingers of both hands, and Raynaud's phenomenon. Blood tests were performed at another hospital, showing elevated levels of anti-nuclear antibodies (ANA), anti-U1-RNP antibodies (> 300 U/mL), and creatine kinase (CK) levels (1,740 U/L). MCTD was suspected, and therefore the patient was referred to our hos-

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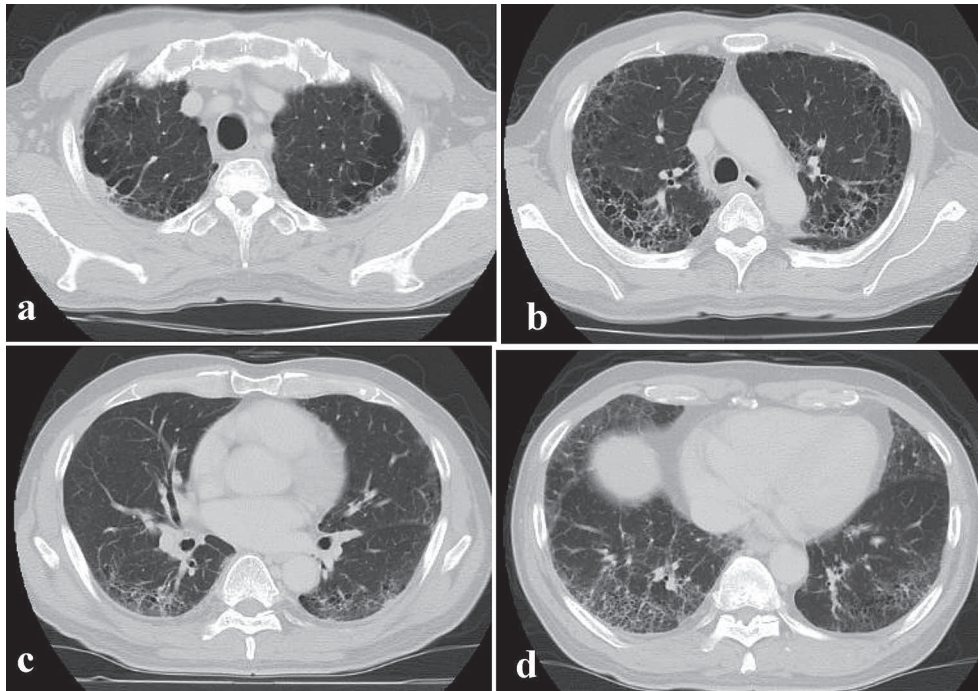


Fig. 1. Chest computed tomography of the lung.

Chest computed tomography (CT) shows ground glass opacity in both lower lungs (b, c, d) with emphysematous changes mainly in the upper lungs (a).

pital for further investigation. The patient was a smoker (25 cigarettes/day for 25 years). On admission, his blood pressure was 101/61 mmHg and body temperature was 36.6°C. Physical examination revealed malar rash, ankyloglossia, swollen fingers, and petechiae around the fingers. Heart sounds were clear; however, fine crackles were audible in both lower lungs. Laboratory data indicated liver dysfunction (aspartate transaminase, 143 U/L; alanine transaminase, 63 U/L), anemia (hemoglobin, 13.0 g/dL), elevated erythrocyte sedimentation rates (31 mm per 1 hour), and elevated CK (1,704 U/L), lactate dehydrogenase (469 U/L), immunoglobulin G (2,819 mg/dL), Kerbs von den Lungen-6 (1,933 U/mL), and C-reactive protein (2.9 mg/dL) levels. The blood creatinine level and urine test were normal. ANA and anti-U1-RNP antibodies were > 2,560 (speckled, homogenous type) and > 240, respectively. A serum ANCA test was positive for MPO-ANCA (161 U/mL), whereas serum anti-glomerular basement membrane (anti-GBM) antibody was negative. Chest X-ray showed reticular shadows in both lower lungs. Chest computed tomography also showed ground glass opacities mainly in both lower lungs with emphysematous changes (Fig. 1). Magnetic resonance imaging (MRI) (short T1 inversion recovery) showed high intensity of the femoral muscles, indicating muscle inflammation (Fig. 2, arrows). Electromyography showed myogenic changes, which confirmed the presence of inflammatory myositis. Skin biopsy from a finger showed thickening of collagen fibers, compatible with features of the limited type of SSc. From these clinical findings, we established a diagnosis of MCTD,

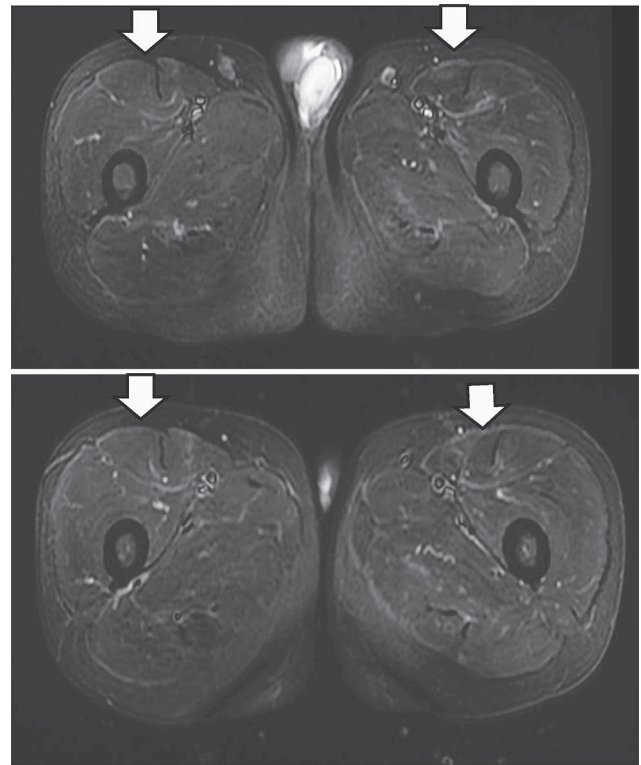


Fig. 2. Femoral magnetic resonance imaging.

Femoral magnetic resonance imaging (MRI) with short T1 inversion recovery images shows high intensity of femoral muscles (arrows), indicating the presence of myositis in both femoral regions.

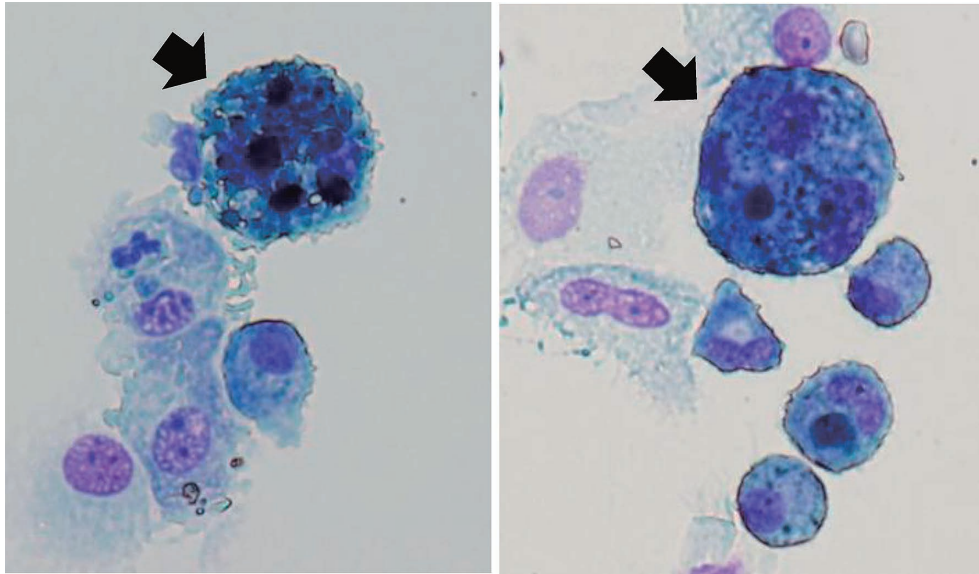


Fig. 3. Presence of hemosiderin-laden macrophages in the bronchoalveolar lavage fluid. Bronchoalveolar lavage fluid (BALF) samples with hemosiderin-laden macrophages (arrows), suggest alveolar hemorrhage (Diff-Quik stain, $\times 400$ magnification).

Clinical course

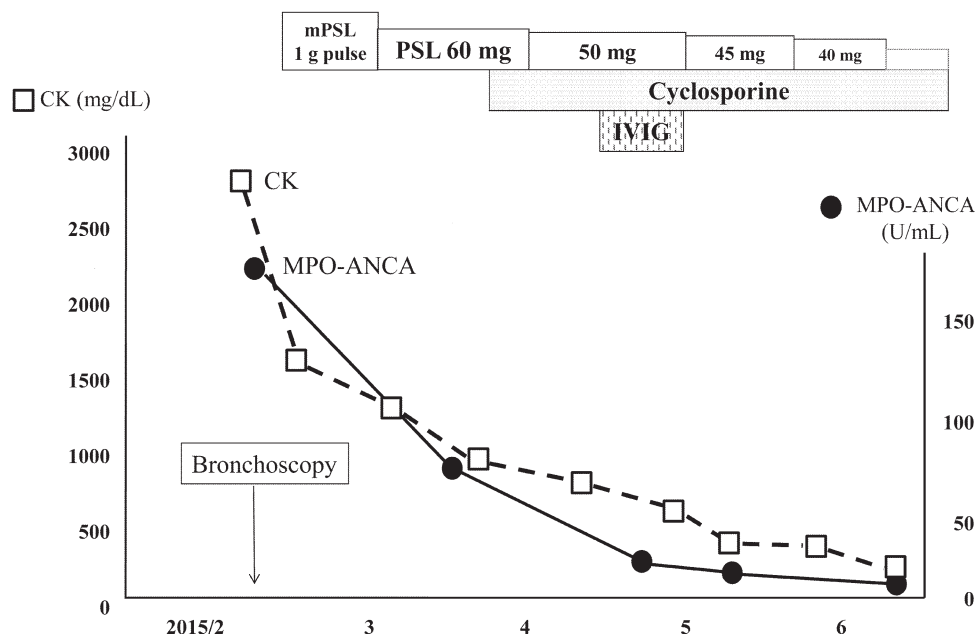


Fig. 4. Overview of the clinical course.

The patient was treated using intravenous methylprednisolone (mPSL) (1 g/day for 3 days), followed by a tapering dose of oral prednisolone (PSL) (60 mg, 50 mg, 45 mg, 40 mg), intravenous immunoglobulin (IVIG) (20 g/day for 5 days), and oral cyclosporine A (150 mg/day). Serum myeloperoxidase-specific anti-neutrophil cytoplasmic antibody (MPO-ANCA) levels and creatine kinase (CK) levels returned to the reference range following these treatments.

according to the diagnostic criteria for MCTD given by the Ministry of Health and Welfare of Japan (Kasukawa 1999), accompanied by elevated MPO-ANCA.

In order to test for progressive interstitial lung disease, bronchoscopy was performed. Hemosiderin-laden macrophages were detected in bronchoalveolar lavage fluid using

Diff-Quik stain (Fig. 3). The percentage of hemosiderin-laden macrophages was 29.4%, which met the criteria for alveolar hemorrhage (Jin et al. 2009). Transbronchial lung biopsy showed mild-to-moderate lung fibrosis, indicating interstitial pneumonia. Other lung diseases causing alveolar hemorrhage, such as Goodpasture's syndrome, infec-

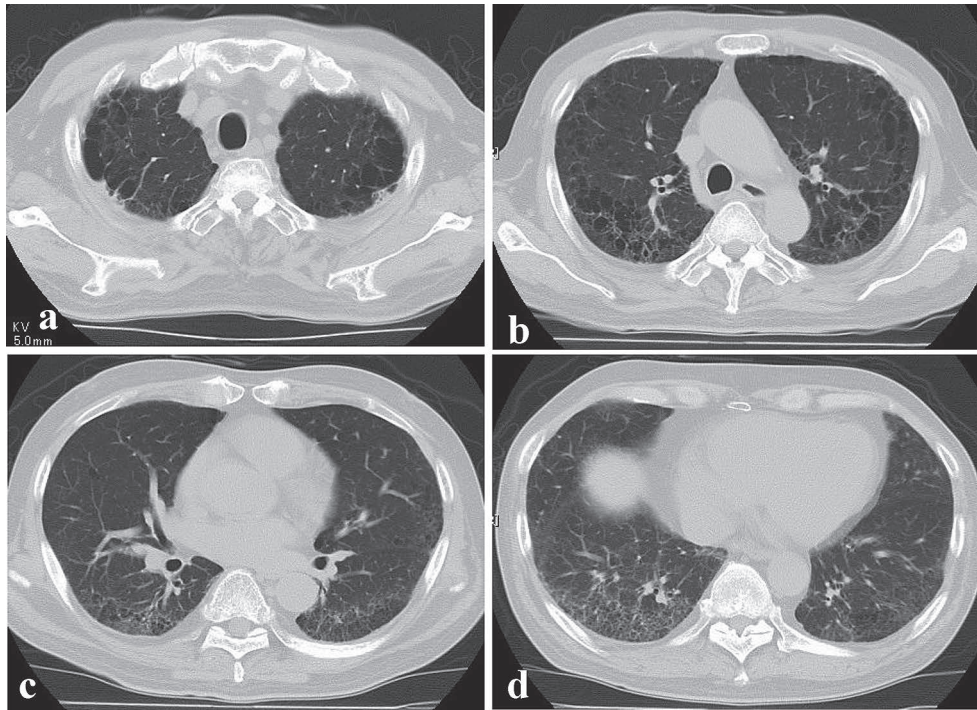


Fig. 5. Computed tomography images of the lung after 3 months of immunosuppressive treatment. Computed tomography images show improvement of ground-glass opacity in both lungs (a, b, c, and d).

tions, drugs, toxic agents, malignancy and heart disease were all denied from his clinical history and condition. Therefore, we suspected that the patient had alveolar hemorrhage accompanied by MPA with progressive interstitial lung disease.

He received methylprednisolone pulse therapy (1 g/day for 3 days) following the oral administration of prednisolone (60 mg/day; Fig. 4). Intravenous immunoglobulin (20 g/day for 5 days) and oral cyclosporine A (150 mg/day) were also administered for interstitial lung disease and steroid-refractory myositis. Subsequently, serum MPO-ANCA levels and CK levels decreased, and prednisolone doses were successfully tapered.

After 3 months of immunosuppressive therapy, CT findings ameliorated (Fig. 5) and lung function test (%vital capacity) improved from 78.1% to 87.1%. To date, no subsequent relapse of disease is observed.

Discussion

This case is considered an example of the rare condition of MCTD accompanied by MPO-ANCA-positive polyangiitis. The diagnosis of MPA was accurate because the patient showed progressive interstitial lung disease with alveolar hemorrhage accompanied by elevated MPO-ANCA levels and substantial inflammation, which meet the criteria for the diagnosis of (probable) MPA, as proposed by a group researching intractable vasculitis and sponsored by the Ministry of Health and Welfare of Japan in 2002 (Ozaki 2007). Our presented case also meets MPA criteria according to the classification algorithm proposed by the

European Medicines Agency (Watts et al. 2007). Interstitial lung disease and myositis were successfully treated with immunosuppressive therapy, resulting in the decrease of MPO-ANCA titers (Fig. 4).

Cases of MCTD complicated with MPA are rarely reported, and only 10 cases (including our case) have been described so far (Inada et al. 1999; Makita et al. 2000; Hernández-Molina et al. 2006; Kitaura et al. 2006; Hong et al. 2010; Murakami et al. 2011; Konstantinov et al. 2013; Murakami et al. 2013; Sun et al. 2014). The clinical features of MCTD with MPA were shown in Table 1. The age at diagnosis of MPO-ANCA-positive vasculitis varied between 38 and 68 years. The rate of female patients was 90%. All patients showed positivity for MPO-ANCA, and one patient (10%) was positive for both MPO-ANCA and PR3-ANCA (Murakami et al. 2013). Inada et al. (1999) reported a case of MCTD complicated with MPA positive for anti-GBM antibodies. The most frequent clinical manifestations were glomerulonephritis and interstitial pneumonia (80% each, respectively). Of note, three of 10 patients (30%) suffered from alveolar hemorrhage, and two of three patients with alveolar hemorrhage died in spite of intensive treatment (Inada et al. 1999; Kitaura et al. 2006). With regard to therapy, all patients received corticosteroids and eight received methylprednisolone pulse therapy. Six patients (60%) received cyclophosphamide and two received azathioprine. Three patients (30%) died during their clinical courses, and the causes of death were diffuse alveolar hemorrhage, interstitial pneumonia exacerbation, and sepsis. These facts indicate that MCTD complicated

Table 1. Clinical features of MCTD associated with MPO-ANCA positive polyangiitis.

Year	Author	Age	Sex	MPO-ANCA	Clinical manifestation	Therapy	Outcome
1999	Inada	46	Female	18 EU	Glomerulonephritis, interstitial pneumonia, alveolar hemorrhage	mPSL, PSL, hemodialysis	dead
2000	Makita	58	Female	118 EU	Glomerulonephritis, interstitial pneumonia	mPSL, PSL, CYP	alive
2006	Hernández-Molina	47	Female	9.3 EU	Glomerulonephritis	mPSL, PSL, CYP	alive
2006	Kitaura	42	Female	132 EU	Glomerulonephritis, interstitial pneumonia, alveolar hemorrhage	mPSL, PSL, CYP, plasmapheresis	dead
2010	Hong	60	Female	34 IU/mL	Glomerulonephritis, interstitial pneumonia	mPSL, PSL, CYP	alive
2011	Murakami	68	Female	59 EU	Glomerulonephritis, pleuritis, sepsis	PSL	dead
2013	Murakami	38	Female	80.3 U/mL	Interstitial pneumonia, mononeuritis multiplex	mPSL, PSL, AZA	alive
2013	Konstantinov	42	Female	789 u/L	Glomerulonephritis	PSL, CYP	alive
2014	Sun	35	Female	159.8 U/mL	Interstitial pneumonia, glomerulonephritis	mPSL, PSL, CYP	alive
2014	Our case	64	Male	161 U/mL	Myositis, alveolar hemorrhage	mPSL, PSL, IVIg, CyA	alive

AZA, azathioprine; CyA, cyclosporine; CYP, cyclophosphamide; IVIg, intravenous immunoglobulin therapy; MPO-ANCA, myeloperoxidase-specific anti-neutrophil cytoplasmic antibody; mPSL, methylprednisolone; PSL, prednisolone.

with MPA occurs predominantly in females, and the main causes of death are lung complications (alveolar hemorrhage and/or progressive interstitial pneumonia) and infection. Also, progressive renal disease (rapidly progressive glomerulonephritis, RPGN) seems to be associated with a severe outcome in such patients. Actually, of all patients with a fatal outcome associated with glomerulonephritis, two of three patients had RPGN (Inada et al. 1999; Kitaura et al. 2006). All patients received corticosteroids, and the major immunosuppressive agent used was cyclophosphamide (60%). These agents were used to ameliorate severe symptoms such as RPGN, interstitial pneumonia, and alveolar hemorrhage. Therefore, proper intensive treatment for MPA symptoms may result in a good outcome in patients with MCTD with MPA.

Interestingly, pulmonary hypertension was not associated with a fatal outcome in our study. Generally, pulmonary hypertension is recognized as a major cause of death (26%) in MCTD patients (Kasukawa 1999). However, the main cause of death in MPA is vasculitis itself and infection (Lane et al. 2005). Although the profound pathogenesis of MCTD complicated with MPA is unknown, the occurrence of systemic vasculitis with MPO-ANCA production may influence the MCTD pathogenesis in such patients. In addition, with regard to ANCA-associated lung fibrosis, MPO-ANCA may be involved in the pathogenesis of interstitial pneumonia progression by oxidative stress through the interaction of MPO with anti-MPO antibodies, as previ-

ously described (Guilpain et al. 2011). As MCTD accompanied by alveolar hemorrhage is much less frequent than that accompanied by MPA (Horiki et al. 1998), lung complications in our case can be strongly associated with MPA activity. In any case, further investigation and the accumulation of such cases are required to understand the pathogenesis of MCTD complicated with MPA.

In conclusion, MCTD may accompany MPA with progressive interstitial lung disease and alveolar hemorrhage. Severe lung complication such as interstitial pneumonia and alveolar hemorrhage may indicate a poor outcome, and prompt immunosuppressive therapy should be performed in such patients.

Conflict of Interest

The authors declare no conflict of interest.

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