Fatal Alveolar Hemorrhage in a Patient with Mixed Connective Tissue Disease Presenting Polymyositis Features

Terumi Horiki, Gentaro Fuyuno*, Makoto Ishii*, Tamotsu Sasa*, Makoto Shibuya**, Noriharu Yanagimachi*** and Yukinobu Ichikawa

A 22-year-old female with Raynaud’s phenomenon, swollen hands and a high titer of anti-RNP antibodies developed fever and myositis. Prednisolone (40 mg/day) was considered effective for myositis since circulating myogenic enzymes rapidly decreased. However, she suddenly developed respiratory distress with bilateral pulmonary infiltrates and bloody sputum. Under the diagnosis of alveolar hemorrhage (AH), intravenous methylprednisolone pulse therapy was given, but she died of respiratory failure. Autopsy findings demonstrated massive AH with hematoma formation, and myositis in the iliopsoas muscle. Depositions of immune complex and vasculitic lesions were not recognized in her lungs.

Key words: collagen disease, myositis, Raynaud’s phenomenon, pulmonary hemorrhage, vasculitis

Introduction

Alveolar hemorrhage (AH) has been reported in at least 70 patients with systemic lupus erythematosus (SLE) including 3 SLE patients associated with mixed connective tissue disease (MCTD) (1-4) (Table 1). In MCTD or polymyositis (PM) patients, interstitial pneumonitis/pulmonary fibrosis is a frequently observed pulmonary involvement. Pulmonary hypertension has also been well recognized in MCTD as a cause of death (5). However, AH seems to be extremely rare in MCTD or PM, since only 6 cases (4 MCTD and 2 PM patients) have been reported so far. Three of the 4 MCTD patients were further complicated with SLE. Thus, the remaining 3 patients (one MCTD patient and 2 PM patients) were not associated with definite SLE or other collagen-vascular disease (4, 6) (Table 1). Here, we described the first case of MCTD presenting PM features and fatal AH, and review the literature of MCTD or PM patients who developed AH.

Case Report

A 22-year-old Japanese female was referred to our hospital because of a 2-year history of Raynaud’s phenomenon on August 15, 1995. She had sausage-like fingers; serological studies demonstrated positive fluorescent antinuclear antibodies (FANA) >1:2,560, speckled pattern and anti-RNP antibodies [202 Index value (IV); N<7.0, enzyme-linked immunosorbent assay (ELISA)] rheumatoid factors (RF; nephelometry) and antibodies to double stranded (ds) DNA, single stranded (ss) DNA, Sm, SS-A/Ro, Scl 70 or Jo-1 antigen were negative. Her immunoglobulin levels were high, but complements were within the normal range. Hematologic studies [white blood cell (WBC), red blood cell (RBC), hemoglobin (Hgb), hematocrit (Ht) and platelet counts], blood chemistries (glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), lactate dehydrogenase (LDH), creatinine kinase (CK), and creatinine), urinalysis and C-reactive protein (CRP) level were within a normal range, and chest radiograph was normal.

On August 28, 1995, she developed a high fever (39°C), sore throat, polyarthralgia and cervical lymphadenopathy, and was treated with diclofenac sodium (75 mg/day) and clarithromycin (400 mg/day). However, her symptoms worsened and she was admitted to our hospital on September 3. Physical findings on admission were as follows: blood pressure 104/60 mmHg, pulse rate 100/min, respiration rate 22/min, and body temperature 38.6°C. Her throat was reddish, and bilateral cervical lymph node swelling (ø 5mm) was recognized with tenderness. Heart murmurs were not audible and lungs were clear. Hepatosplenomegaly, leg edema, skin rash or sclerosis, and joint swelling were not observed. Myalgia with muscle tenderness...
Table 1. Pulmonary Alveolar Hemorrhage in MCTD or PM

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/ Sex</th>
<th>Duration of MCTD or PM</th>
<th>Criteria of MCTD or PM</th>
<th>CIC Cr mg/dl</th>
<th>P/t x10^9/μl</th>
<th>Diagnosis of AH</th>
<th>Pathological findings in the lungs other than AH</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MCTD* [1]</td>
<td>37/M</td>
<td>9Y</td>
<td>esophageal hypomotility, arthritis</td>
<td>+ 2.6</td>
<td>9.3</td>
<td>hemoptysis</td>
<td>n.d.</td>
<td>steroid pulse, HDPEPx</td>
<td>alive</td>
<td>MCTD* SLE (ANA/ arthritis/encephalitis/ nephritic syndrome)</td>
</tr>
<tr>
<td>2. MCTD* [2]</td>
<td>31/F</td>
<td>2Y</td>
<td>leukocytopenia, restrictive pulmonary dysfunction</td>
<td>+ 1.3</td>
<td>14.1</td>
<td>BAL</td>
<td>n.d.</td>
<td>steroid</td>
<td>alive</td>
<td>MCTD* SLE (ANA/ anti-DNA Ab/leukopenia/ encephalitis)</td>
</tr>
<tr>
<td>4. MCTD* [4]</td>
<td>52/F</td>
<td>6M</td>
<td>thrombocytopenia, restrictive pulmonary dysfunction</td>
<td>– 0.7</td>
<td>3.5</td>
<td>BAL</td>
<td>n.d.</td>
<td>diuretics, AZA, steroid</td>
<td>alive</td>
<td>MCTD* SLE (ANA/BFP/AIHA/mythocytopenia/thrombocytopenia)</td>
</tr>
<tr>
<td>5. PM [6]</td>
<td>39/M</td>
<td>2w</td>
<td>muscle weakness, CK T, myopathic EMG</td>
<td>n.d. WNL</td>
<td>65.3</td>
<td>lung biopsy</td>
<td>capillaritis with extensive neutrophilic &amp; round cell infiltration of alveolar walls</td>
<td>steroid, CYC</td>
<td>alive</td>
<td>anti-Jo-1 antibody (+)</td>
</tr>
<tr>
<td>6. PM [6]</td>
<td>68/F</td>
<td>1w</td>
<td>muscle weakness, CK T, myopathic EMG</td>
<td>n.d. 0.9 n.d.</td>
<td>TBLB</td>
<td>capillaritis with organizing pneumonia</td>
<td>steroid, CYC</td>
<td>alive</td>
<td>MCTD+</td>
<td></td>
</tr>
<tr>
<td>7. MCTD* our case</td>
<td>22/F</td>
<td>2Y</td>
<td>muscle weakness, CK T</td>
<td>– 0.8</td>
<td>17.8</td>
<td>BF and autopsy</td>
<td>IP, IF: negative</td>
<td>steroid pulse</td>
<td>dead</td>
<td>MCTD+ myositis</td>
</tr>
</tbody>
</table>


*These cases had Raynaud’s phenomenon, sausage-like fingers and high titers of anti-RNP antibodies, but anti-RNP antibodies were not detected in case 1 when alveolar hemorrhage developed.

was detected on her gastrocnemius and deltoid muscles, and symmetric proximal muscle weakness was revealed on her extremities.

Laboratory studies on admission are shown in Table 2. She had leukocytosis (WBC 10,400/μl), lymphocytopenia (104/μl) and thrombocytopenia (7.3×10^3/μl). Coagulation studies were normal except for fibrin/fibrinogen degradation product (FDP 383 mg/dl). Circulating myogenic enzyme levels (GOT 183 U/l, LDH 2,272 U/l, CK 2,472 U/l and aldolase 25.8 U/l) and myoglobin (290 mg/ml) were high. Serum CRP level (4.02 mg/l) was elevated, but complement levels and circulating immune complex level (by Clq solid-phase enzyme immunoassay) were within the normal range. Anti-phospholipid antibodies [anti-cardiolipin β2-glycoprotein I (CL β2GPI) antibodies, screening for lupus anticoagulants (LA) determined by dilute platelet aggregometry and venereal disease research laboratory test (VDRL)], anti-glomerular basement membrane (GBM) antibodies and anti-neutrophil cytoplasmic antibodies (ANCA) including antibodies to myeloperoxidase (MPO) and proteinase 3 (PR3) were negative. Throat bacterial culture was positive for Candida albicans, and urine culture detected Streptococcus epidermidis (107/ml), but serum Candida antigens measured by latex agglutination test and repeated blood culture were negative. Serum immunoglobulin G (IgG) antibodies to herpes simplex (57.6 IV; ELISA) and herpes zoster virus (16.5 IV; ELISA) were positive, but the other viral antibodies examined were negative. Chest X-ray revealed mild cardiomegaly (CTR 50.0%), but electrocardiogram and echocardiogram were normal, except for a slightly elevated pulmonary artery pressure (40.8 mmHg). Arterial blood gas analysis under oxygen inhalation by nasal canula (O2 11/min) showed respiratory alkalosis (pH 7.461, pO2 99 mmHg, pCO2 26.6 mmHg, HCO3" 19.1 mmol/l, BE –2.5 mmol/l).

Under the diagnosis of MCTD presenting acute PM features, she had received intravenous prednisolone (40 mg/day) since the 2nd day of her admission. Blood myogenic enzyme levels and thrombocytopenia promptly improved (Fig. 1). On the 5th day of admission, however, she suddenly developed respiratory distress with strong dyspnea and dry cough. Chest X-ray demonstrated bilateral pulmonary infiltrates and pleural effusion (Fig. 2). Rapid progression of anemia (hemoglobin levels from 13.5 to 10.8 g/dl during subsequent 36 hours), was observed although her platelet count (17.8×10^4/jnl) was normal, and mucocutaneous bleeding tendency was not recognized. On the 6th day of admission, she was intubated for the management of respiratory conditions. At that time, AH was strongly suspected since bronchofiberscopy demonstrated massive bloody sputum. Repeated cytologic studies for her sputum did not detect hemosiderin-laden macrophages. Her pulmonary status temporarily improved by the mechanical respiratory support.
She received further intravenous methylprednisolone pulse therapy (1 g/day, for 3 days), but the episodes of AH were repeated. Thoracic computed tomography (CT) obtained on September 18 (16th day of admission), demonstrated air-space consolidations in bilateral lung fields. On MR imaging, performed on September 30, the consolidative areas showed high signal intensities on T1-weighted images and mixed high and low signal intensities on T2-weighted images (Fig. 3). She eventually developed sepsis (Burkholderia cepacia) and died of progressive respiratory failure caused by repeated AH on October 20.

Autopsy findings demonstrated diffuse pulmonary AH with microscopic fibrosis and scattered subpleural hematoma formations (Figs. 4, 5), and Enterobacter cloacae was cultured from a part of a hematoma. Immune complex depositions and vasculitis were not detected in her lungs. Random muscle fiber
Alveolar Hemorrhage in MCTD

Intubation Intubation Extubation

Methylprednisolone 1,000 mg
Prednisolone 40 mg 35 mg

Figure 1. Clinical course during hospitalization. BT: body temperature, Hgb: hemoglobin.

atrophy with mononuclear cell infiltration compatible with polymyositis was detected in iliopsoas muscles. No pathological findings were observed in the kidneys, although onion-skin appearance of arterioles was seen in the spleen.

Discussion

The present case had Raynaud's phenomenon and sausage-like fingers with positive anti-RNP antibodies. Circulating myogenic enzymes were markedly elevated, when she developed muscle weakness. In addition, she had transient lymphocytopenia, thrombocytopenia, polyarthralgia and lymphadenopathy. These clinical pictures fulfill the MCTD criteria proposed by the Japanese Research Committee (7), although the definition of MCTD is still controversial. We did not

Figure 2. Chest X-ray obtained on September 8 (the first episode of alveolar hemorrhage): bilateral infiltrative shadow and pleural effusion were recognized.
Figure 3. MR imaging, performed on September 30: consolidation areas showed high signal intensities on T1-weighted images (A) and mixed high and low signal intensities on T2-weighted images (B), respectively.

perform electromyographic studies, but she had predominant PM-like features as demonstrated by autopsy findings, symmetric muscle weakness and elevated muscle enzymes (8).

Alveolar hemorrhage syndrome was previously classified by Leatherman et al (9), and includes anti-GBM antibody disease, idiopathic pulmonary hemosiderosis, collagen-vascular diseases and systemic vasculitides, idiopathic rapidly progressive glomerulonephritis, and AH due to exogenous agents such as candida (10), aspergillus (11), legionella and cytomegalovirus (12) infections. In addition, ANCA [anti-MPO antibodies (13) and anti-phospholipid antibodies (14)] have recently been shown to be related to AH.

Of collagen-vascular diseases, AH has been mainly reported in SLE patients and at least 70 such SLE cases have been described to date. In these SLE patients, AH was frequently associated with renal failure/heart failure, coagulopathy/thrombocytopenia, infections, autoimmune hemolytic anemia and vasculitis/vasculopathy. Histopathologically pulmonary vasculitis was detected in 21% and depositions of immune complex in the alveolar tissue were observed in 61% of the SLE patients (3, 10-12, 15).

Figure 4. Left lung at autopsy showed alveolar hemorrhage with scattered subpleural hematomas (small arrows), and bullous formation (large arrowhead) accompanied by hemothorax, pyothorax and pneumothorax.

Figure 5. Microphotograph of the lung parenchyma: alveolar spaces were occupied by erythrocytes, fibrin, and hemosiderin-laden macrophages (HE stain, ×150).
Alveolar Hemorrhage in MCTD

Of dermatomyositis and polymyositis patients, interstitial lung disease was detected in 17.4% by chest X-ray (16), but only one report described two cases of AH associated with PM (6). Pathological findings of the patients were extensive pulmonary capillarities and bronchiolitis obliterans organizing pneumonia, respectively (Table 1). One case was positive for anti- Jo-1 antibodies, but antibodies to GBM or ANCA were absent in both cases.

On the other hand, the frequent pulmonary complications recognized in MCTD, pulmonary interstitial disease (30%) and pulmonary hypertension (29%) have been detected by chest X-ray or right heart catheterization studies (17). However, AH is extremely rare in MCTD patients, and only 4 cases have been reported to date. In addition, 3 of the 4 MCTD cases fulfilled the SLE criteria (18) and the remaining case had SLE-like disease with positive FANA and a biologically false-positive result for serological tests of syphilis, autoimmune hemolytic anemia, lymphocytopenia and thrombocytopenia (1, 3) (Table 1).

The present case did not fulfill the SLE criteria, but presented PM features. She was negative for any antibodies associated with AH such as anti-GBM antibodies, MPO-ANCA and antiphospholipid antibodies, and autopsy studies did not reveal vasculitis or immune complex depositions in the pulmonary alveolar tissues. However, the onion-skin appearance of arterioles recognized in her spleen may indicate possible systemic vasculitis which might have been modified by methylprednisolone pulse therapy. The interstitial pneumonitis observed in this case was likely due to oxygen inhalation at a high concentration and/or secondary effects of AH, because the thoracic CT obtained during her clinical course did not reveal interstitial findings. We considered that infection was not the primary cause for the episodes of AH in this case, but hematomas which ruptured into the bronchiole/intrathoracic space were infected during the clinical course.

AH is generally a life-threatening complication, and early clinical diagnosis is important. In the present case, AH was strongly suspected by the abrupt onset of dyspnea, bloody sputum, rapid progression of anemia and infiltrative shadows on chest X-ray. However, hemosiderin-laden macrophages, which are diagnostic for AH, could not be detected by repeated cytologic studies of her sputum. Bronchoalveolar lavage is also known to be useful for the diagnosis of AH, but we could not perform the procedure due to her critical condition. Thoracic CT and magnetic resonance (MR) examinations of this case demonstrated so-called pulmonary parenchymal lesions in the area of AH, although the MR imaging findings were not identical to the previously reported findings of AH (19): preferential T2 shortening caused by the paramagnetic effects of ferric iron in the hemorrhaged lesions.

The mortality rate of SLE patients with AH was reduced to 40% (14/35) during the recent 10 years (1986–1995) compared with the period between 1976 and 1985 (62%, 21/34). In consideration of the comparison between the two periods, steroid pulse therapy (23 vs. 9 cases), cyclophosphamide (CYC; including CYC pulse therapy, 12 vs. 4 cases) and plasma exchange (9 vs. 2 case) have more frequently been employed in the recent 10 years. Survival rate for each treatment was 52% (12/23, steroid pulse therapy), 80% (8/10, CYC including pulse therapy), and 44% (4/9, plasma exchange). Furthermore, advances in the recent supportive therapies and early diagnosis of AH are also considered to contribute to the improved prognosis of AH. Retrospectively, steroid pulse therapy performed in our case was not effective for AH, but additional immunosuppressive therapies were not given to prevent further pulmonary infections. Plasma exchange was not considered, since circulating immune complexes and autoantibodies associated with AH were not detected.

References

