Disseminated Intravascular Coagulation Associated with Pulmonary Tuberculosis

Masaki Fujita***, Ritsuko Kunitake***, Yoshiki Nagano* and Fumihiko Maeda*

Disseminated intravascular coagulation (DIC) is a very rare complication of pulmonary tuberculosis. We herein describe a case of cavitary tuberculosis complicated with DIC. Rifampin was considered to deteriorate the clinical course of DIC in this case.

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Introduction

Disseminated intravascular coagulation (DIC) is considered to be an emergency life-threatening problem in the internal medicine field. DIC is typically associated with underlying disease such as an infection or a malignancy. Miliary tuberculosis is well known to cause DIC, while pulmonary tuberculosis seldom causes DIC. Here, we report a case of DIC complicated with pulmonary tuberculosis. This case showed an interesting clinical course of DIC associated with anti-tuberculous therapy.

Case Report

A 43-year-old man was referred to our hospital for anti-tuberculous therapy. His chest roentgenography on admission (Fig. 1) showed left apical cavitary change, infiltrates predominantly in the left lung field, and nodules on the right apex. There were many acid-fast bacilli in his sputum. On admission both liver dysfunction (aspartate aminotransferase: 103 U/l, alanine aminotransferase: 53 U/l, and hepatitis C virus antibody: positive) and thrombocytopenia (platelet: 32,000/mm³) were observed. White blood cell count was slightly elevated (10,900/mm³). Other laboratory data were as follows: red blood cell count 429 x 10⁶/mm³, hemoglobin 12.1 g/dl, hematocrit 36.3%, and C-reactive protein 11.9 mg/dl. The physical examination showed no tendency of bleeding. The findings of chest computed tomography (Fig. 2), ocular fundus, and bone marrow tapping revealed no evidence of miliary tuberculosis.

We started anti-tuberculous therapy with isoniazid (400 mg/day), rifampin (450 mg/day), and streptomycin (1 g/day, twice a week). When we noticed a bleeding tendency, his thrombocytopenia had already progressed (13,000/mm³) at one week after start of the therapy. Laboratory data supported the diagnosis of DIC (prothrombin time 12.9 seconds, partial thromboplastin time 44.9 seconds, fibrin degradation products above 40 µg/ml, fibrinogen 473 mg/dl, D-dimer 1,235 µg/ml, and platelet associated IgG negative). We could differentiate his thrombocytopenia from liver cirrhosis by abdominal ultrasonography.

Heparin was started as anti-coagulant therapy (10,000 U/}

Figure 1. Chest roentgenogram on admission.
DIC and Pulmonary Tuberculosis

day). Since the possibility of rifampin-induced thrombocytopenia was considered, we discontinued rifampin as well as the intramuscular injection of streptomycin. Then we started ethambutol (1 g/day) and pyrazinamide (1.5 g/day) in place of these drugs. A few days after the start of this therapy, his platelet counts slightly increased (platelet; 26,000/mm³). Since therapy for the underlying disease is essential for DIC, we started rifampin again. Although the anti-coagulant therapy was continued, his platelet counts decreased again (platelet; 15,000/mm³). The platelet counts increased again after we stopped rifampin (platelet; 28,000/mm³). We could observe his clinical course without administering heparin.

Thereafter, we re-started rifampin at a dose of 300 mg/day. There was no apparent effect of rifampin on the platelet counts at this dose without the anti-coagulant therapy (platelet; 29,000/mm³). After we increased the dose of rifampin, however, DIC progressed (platelet 18,000/mm³, prothrombin time 12.7 seconds, partial thromboplastin time 62.4 seconds, fibrin degradation products between 10 and 40 μg/ml, fibrinogen 514 mg/dl). Thus we returned rifampin to 300 mg/day and re-started the anti-coagulant therapy (heparin; 10,000 U/day). Eventually his platelet counts increased after the improvement of tuberculosis was achieved (platelet; 101,000/mm³). The clinical course is summarized in Fig. 3. In addition, the hematologic data during

<table>
<thead>
<tr>
<th>INH</th>
<th>PZA</th>
<th>SM</th>
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Figure 3. Clinical course. The relationships between the platelet counts and the drugs are shown. INH: isoniazid, PZA: pyrazinamide, SM: streptomycin, EB: ethambutol, RFP: rifampin. The platelet counts tended to decrease after the start of rifampin. The hematologic data from Dec. 15 to Jan. 29 are shown in Table 1.

Table 1. Hematologic Data during the Early Phase of DIC

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<tbody>
<tr>
<td>Rifampin (mg/day)</td>
<td>450</td>
<td>—</td>
<td>450</td>
<td>—</td>
<td>—</td>
<td>300</td>
<td>450</td>
</tr>
<tr>
<td>Heparin (×10⁴ U/day)</td>
<td>—</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Platelet (×10⁵/mm³)</td>
<td>1.3</td>
<td>2.6</td>
<td>1.5</td>
<td>2.8</td>
<td>3.2</td>
<td>2.9</td>
<td>1.8</td>
</tr>
<tr>
<td>FDP (μg/ml)</td>
<td>&gt;40</td>
<td>&lt;10</td>
<td>10-40</td>
<td>&lt;10</td>
<td>NT</td>
<td>10-40</td>
<td>10-40</td>
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<tr>
<td>PT (seconds)</td>
<td>12.9</td>
<td>12.7</td>
<td>12.9</td>
<td>12.9</td>
<td>NT</td>
<td>12.4</td>
<td>12.7</td>
</tr>
<tr>
<td>APTT (seconds)</td>
<td>44.9</td>
<td>44.2</td>
<td>44.9</td>
<td>44.1</td>
<td>NT</td>
<td>41.6</td>
<td>62.4</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>473</td>
<td>486</td>
<td>473</td>
<td>486</td>
<td>NT</td>
<td>461</td>
<td>514</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>1,235</td>
<td>NT</td>
<td>NT</td>
<td>426</td>
<td>NT</td>
<td>636</td>
<td>1,408</td>
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NT: not tested, FDP: fibrin degradation products, PT: prothrombin time, APTT: activated partial thromboplastin time.
the early phase of DIC is summarized in Table 1.

**Discussion**

The incidence of tuberculosis has recently been increasing throughout the world (1). In Japan more than 50,000 people are registered as new tuberculosis patients every year. DIC is a rare complication of tuberculosis, however, it is an emergency life-threatening problem. Most cases of DIC associated with tuberculosis are miliary tuberculosis (2). Only a few cases of DIC complicated with pulmonary tuberculosis have been reported (3–6). Although there was no evidence of miliary tuberculosis, DIC began in the present case.

There has been some discussion about the etiology of DIC associated with tuberculosis. Some investigators speculate that a certain material, which includes lipopolysaccharide of *Mycobacterium tuberculosis*, and thromboplastin resulting from tissue necrosis, are responsible for DIC (2, 7). We could not explain why DIC was complicated with cavitary tuberculosis in the present case. Further study, including the pathogenesis of *M. tuberculosis*, is needed to clarify the correlation between tuberculosis and DIC.

Interestingly rifampin deteriorated DIC in this case. Rifampin is known to cause thrombocytopenia and DIC induced by rifampin has also been reported (8). Stein and Libertin reported that most cases of the coagulopathy associated with tuberculosis began after the start of therapy (5). Since rifampin has bactericidal effect for *M. tuberculosis*, we agree with the speculation that rifampin produces a large amount of the causative materials for DIC from *M. tuberculosis* (2, 6). However, Goldfine et al (7) considered that *M. tuberculosis* does not produce any causative materials for DIC, such as endotoxin. In addition, an immunologic reaction of rifampin might play a role in thrombocytopenia. Certainly the role of rifampin in thrombocytopenia remains unclear.

Treatment of the underlying disease is the first line approach to DIC and rifampin is one of the most important drugs in the treatment of tuberculosis. We conclude that some special attention is needed for anti-tuberculous therapy in the tuberculosis patients with DIC.

**References**