Successful Treatment of Severe Lung Hemorrhage Caused by Acquired Factor V Inhibitor with Rituximab

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Abstract

Acquired coagulation factor deficiency is a rare disorder that occurs in patients with drug reactions, malignancy and collagen diseases as well as during pregnancy. Most cases are caused by factor VIII inhibitors. We herein describe the case of a 61-year-old Japanese man with acquired factor V inhibitor who developed symptoms 11 days after lung surgery for empyema. The patient required mechanical ventilation to treat acute respiratory failure due to severe pulmonary hemorrhage. He responded poorly to steroid pulse therapy; however, treatment with rituximab was successful.

Key words: acquired factor V inhibitor, pulmonary hemorrhage, rituximab


Introduction

Acquired coagulation factor deficiency is a rare bleeding disorder caused by the presence of coagulation factor inhibitors, with an estimated incidence of approximately one per million individuals per year (1). The mortality rate of acquired hemophilia A is 10-20% (2). Treatment with steroid and rituximab therapy is recommended to suppress the titer of autoantibodies. Bypass therapy with activated factor VII is used in severe cases of hemorrhage in the brain, lungs and gastrointestinal tract (3). To date, only a few cases of acquired deficiency of multiple coagulation factors associated with the presence of inhibitors have been reported (4). We herein report the clinical course of a patient with acquired factor V inhibition who developed severe pulmonary hemorrhage 11 days after undergoing surgery for empyema. Steroid pulse therapy was ineffective, and the patient became critically ill with acute respiratory failure due to worsening pulmonary hemorrhage. Therefore, he was treated with rituximab. His laboratory data became normal six days after the initial treatment with rituximab, and he has remained free from relapse for at least one year.

Case Report

A 61-year-old man was admitted to our hospital for thoracoscopic pleural curettage surgery for the treatment of empyema. Ampicillin/sulbactam (ABPC/SBT) was administered after the procedure. Eleven days after surgery, he suddenly presented with dyspnea and hemoptysis. A physical examination showed pale-colored conjunctivae and petechiae in the oral cavity. The patient’s lung sounds were coarse in the right chest. Ecchymosis was observed around the right elbow, with petechiae on both legs. A blood test demonstrated normocytic anemia. A blood coagulation study demonstrated prolongation of both the prothrombin time (PT) and activated partial thromboplastin time (APTT). As the patient had exhibited normal PT and APTT values before surgery, we concluded that the coagulopathy was acquired. A chest X-ray showed a massive infiltrative shadow in the right pulmonary lobe, suggesting alveolar hemorrhage (Fig. 1).

The presence of acquired inhibitors of coagulation factors was suspected, and a cross-mixing test using serum from the patient and a healthy volunteer was performed. The PT and APTT curves were upward convex in shape (Fig. 2), thus indicating the presence of coagulation factor inhibitors. Tests for lupus anticoagulant and cardiolipin antibodies were both
Figure 1. Chest X-ray demonstrated pulmonary hemorrhage 11 days after surgery for empyema.

Table. Coagulation Factors and Inhibitors

<table>
<thead>
<tr>
<th>Coagulation factors</th>
<th>Activity (%)</th>
<th>Inhibitors (BU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>&lt;3</td>
<td>5</td>
</tr>
<tr>
<td>V</td>
<td>&lt;3</td>
<td>83</td>
</tr>
<tr>
<td>VII</td>
<td>6</td>
<td>nt</td>
</tr>
<tr>
<td>VIII</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>IX</td>
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<td>4</td>
</tr>
<tr>
<td>X</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>XI</td>
<td>&lt;3</td>
<td>4</td>
</tr>
<tr>
<td>XII</td>
<td>&lt;3</td>
<td>4</td>
</tr>
</tbody>
</table>

BU: Bethesda Unit, nt: not tested

Discussion

Acquired coagulation deficiency due to the presence of inhibitors is rare and sometimes life-threatening. Despite the fact that numerous cases of factor VIII inhibitor and more than 100 cases of factor V inhibitor have been reported (5), there are only a few case reports of deficiency of coagulation factors due to the presence of other inhibitors (4). Interestingly, we detected multiple inhibitors for a broad range of coagulation factors (Table). We acknowledge the possibility of false-positive results for coagulation factor inhibitors.
(6,7), as the level of factor V inhibitor was 83 BU/mL, which was much higher than that of the other inhibitors (Table). It has been previously reported that some factor VIII inhibitors cross-react with other coagulation factors (8).

Surgery, drugs, malignancy, child birth and autoimmune disorders are known to be possible causes of the presence of acquired coagulation factor inhibitors (9). In the present case, bacterial infection, surgery and the use of antibiotic therapy may have contributed to the onset of this disease. Although there are several reports of acquired factor V deficiencies caused by the administration of bovine thrombin during surgery to stop bleeding (5, 10), this treatment was not used in the present case during surgery for empyema. Antibiotics, especially β-lactams, are well-known causes of acquired hemophilia (11), and our patient received ABPC/SBT after surgery. However, it remains to be elucidated how factor V inhibitor was induced in this case.

Rituximab is an anti-CD20 antibody that is used to treat B cell malignancies. Recent studies have demonstrated that rituximab is also effective for a number of autoantibody-mediated diseases, including thrombotic thrombocytopenic purpura (12), autoimmune hemolytic anemia (13), immune thrombocytopenia (14) and the presence of acquired factor VIII antibodies (15). Rituximab has been used in three patients with severe and symptomatic disease due to the presence of acquired factor V inhibitor (5). In the present case, the patient became critically ill due to the progression of pulmonary hemorrhage following treatment with steroid pulse therapy. He was successfully treated with rituximab, and has remained in complete remission for at least one year. As the number of cases of acquired coagulation factor deficiency is low, it is therefore necessary to evaluate the efficacy, safety and optimal dosage of rituximab in such patients in future clinical trials.

The authors state that they have no Conflict of Interest (COI).

References


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