Streptococcus pneumoniae-Associated Hemolytic Uremic Syndrome in a Splenectomized Adult Patient

Nobuki Maki, Atsushi Komatsuda, Hiroshi Ohtani, Jun Kuroki, Tamio Nishinari, Kenichi Asakura, Kenichi Sawada and Hideki Wakui

Abstract

A 62-year-old splenectomized woman was admitted because of upper respiratory tract symptoms, general fatigue, and purpura. Laboratory data demonstrated microangiopathic hemolytic anemia, thrombocytopenia, acute renal failure, and a positive Streptococcus pneumoniae (SP) urinary antigen test. A renal biopsy showed thrombotic microangiopathic changes. She was diagnosed with hemolytic uremic syndrome (HUS) secondary to SP infection. Methylprednisolone pulse therapy in addition to antibiotic therapy led to prompt improvement of her symptoms and laboratory abnormalities. This is the first adult case of SP-associated HUS successfully treated without hemodialysis. SP infection should be considered as a causative etiology in all splenectomized patients with HUS.

Key words: adult patient, hemolytic uremic syndrome, postsplenectomy infection, renal biopsy, steroid pulse therapy, Streptococcus pneumoniae

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Introduction

Hemolytic uremic syndrome (HUS) is an acute disease characterized by nonimmune (Coombs negative) microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure (1, 2). In children, typical HUS or post-diarrheal HUS is commonly triggered by Shiga-like toxin-producing Escherichia coli (1, 2). On the other hand, atypical HUS (aHUS) defines non Shiga-like toxin-associated HUS, including Streptococcus pneumoniae-associated HUS (SP-HUS) (1, 2). SP-HUS is a rare but severe complication of invasive SP infection, with a poor clinical outcome when compared with typical HUS (3). SP-HUS usually occurs in neonates and in children less than 5 years of age (2, 3). To our knowledge, only 4 adult cases have been reported in the English language literature and abstracts (4-7).

Splenectomized patients have a high risk for severe infection. In overwhelming postsplenectomy infection syndrome, encapsulated organisms such as SP are particularly important pathogens (8). Herein, we report a splenectomized adult patient who developed SP-HUS. A renal biopsy showed typical findings of thrombotic microangiopathy. In this case, steroid pulse therapy in addition to antibiotic therapy led to prompt improvement of HUS.

Case Report

A 62-year-old woman was admitted because of general fatigue. At the age of 51, she was diagnosed with advanced gastric cancer, and underwent total gastrectomy with splenectomy. Around 1 week prior to admission, she developed upper respiratory tract symptoms, and was treated with non-steroidal anti-inflammatory drug and antibiotic (cefcapene pivoxil hydrochloride). There was no diarrheal prodrome. On admission, her body temperature was 36.9°C. A physical examination showed purpura on her face and legs, and mild pretibial edema. There were no abnormalities in the lungs, heart, and abdomen, except for surgical scars. Urinalysis showed proteinuria (1.0 g/g creatinine) and hematuria (red blood cells 20-29/high-power field). Urinary β2-microglobulin was 41,770 μg/L. Fractional excretion of so-
anti-neutrophil cytoplasmic antibody (ANCA), proteinase 3- and haptoglobin <7 mg/dL. Both direct and indirect Coombs test were negative. Antinuclear antibody, myeloperoxidase-anti-neutrophil cytoplasmic antibody (ANCA), proteinase 3-

Figure 1. Clinical course. The patient was initially treated with minocycline and gabexate mesilate. After methylprednisolone pulse therapy followed by oral prednisolone therapy, laboratory abnormalities improved markedly. Abbreviations: Cre: creatinine, CRP: C-reactive protein, Hb: hemoglobin, LDH: lactate dehydrogenase, m-PSL: methylprednisolone, PC: platelet concentrate, Plt: platelet count, PSL: prednisolone, RCC: red blood cell concentrate.

dium was 2.04%. The hemoglobin was 12.9 g/dL, white blood cell count 12,700/μL, and platelet count 67,000/μL. Prothrombin time was 12.3 sec (prothrombin time-international normalized ratio 1.09), activated partial thromboplastin time 42.1 sec, plasma fibrinogen 273 mg/dL, and fibrin/fibrinogen degradation products (FDP) >80 μg/mL. Serum total protein was 6.1 g/dL, albumin 3.6 g/dL, blood urea nitrogen 54.5 mg/dL, creatinine 4.34 mg/dL, total bilirubin 1.19 mg/dL, aspartate aminotransferase 354 U/L, alanine aminotransferase 149 U/L, lactate dehydrogenase (LDH) 1,582 U/L, sodium 134 mEq/L, potassium 3.4 mEq/L, and chloride 99 mEq/L. Serum IgG was 823 mg/dL, IgA 177 mg/dL, IgM 27 mg/dL, CH50 46.0 U/mL, C3 72 mg/dL, C4 29 mg/dL, C-reactive protein (CRP) 25.87 mg/dL, and haptoglobin <7 mg/dL. Both direct and indirect Coombs tests were negative. Antinuclear antibody, myeloperoxidase-ANCA, and anti-glomerular basement membrane antibody were negative. A chest radiograph showed no abnormal findings.

The clinical course is shown in Fig. 1. After admission, she did not develop neurological disorders or fever. Upper respiratory tract infection and disseminated intravascular coagulation (DIC) was considered according to the diagnostic criteria for DIC (9). She was initially treated with minocycline hydrochloride (200 mg/day) and gabexate mesilate (1,000 mg/day). Although serum CRP levels decreased promptly, rapidly worsening thrombocytopenia and anemia with elevated serum LDH levels were observed. Peripheral blood smear examination revealed schistocytes and acanthocytes (Fig. 2). A bone marrow aspiration showed no findings of hemophagocytosis or malignancy. ADAMTS13 (a disintegrin-like metalloprotease with thrombospondin type 1 motifs 13) activity, which was measured at Nara Medical University (10), was 46% of normal. SP antigen was detected in a urine specimen by the Binax NOW SP antigen test (Binax Inc., Portland, ME, USA).

Her renal function worsened rapidly. To determine the cause of acute renal failure, a renal biopsy was performed after platelet transfusion. The biopsy specimen contained 16 glomeruli, 1 of which was sclerotic. Light microscopy showed diffuse narrowing of glomerular capillary lumens due to swelling of injured endothelial cells, segmental thrombi in 4 glomeruli, and cellular crescents in 2 glomeruli (Fig. 3). Thrombi in the arteriole at the glomerular hilus were also observed. No severe vascular lesion, such as fibrinoid necrosis, was found. Focal tubular necrosis and infiltration of small round cells were seen. Immunofluorescence microscopy showed no immunoglobulin or complement deposits. Electron microscopy revealed glomerular endothelial cell swelling without marked widening of the subendothelial space (Fig. 4). These histological findings were comparable with thrombotic microangiopathy.

On the basis of the clinical, laboratory, and histological findings, she was diagnosed with HUS secondary to SP infection. Because a systemic proinflammatory cytokine response was considered to be involved in her clinical condition, she was treated with methylprednisolone pulse therapy followed by oral prednisolone therapy, in addition to initial treatments. Thereafter, her symptoms and laboratory abnormalities improved markedly without dialysis. She was discharged at 36 days after admission, and steroid therapy was tapered in the outpatient clinic. She received pneumococcal vaccine 6 months later. Sixteen months later, urinalysis was normal, and serum creatinine was 0.85 mg/dL. A follow-up renal biopsy showed minor glomerular abnormalities. There were mild to moderate arterio-arteriolar sclerosis and chronic interstitial fibrosis. Steroid therapy was discontinued. Recurrence of HUS was not observed for 3 years.

**Discussion**

In the present patient, the diagnosis of aHUS was made...
based on the triad of clinical findings (1, 2): nonimmune microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure, in the absence of a diarrheal prodrome. As the cause of aHUS, SP infection was suspected because of the past history of splenectomy and clinical symptoms. This possibility was confirmed by the Binax NOW SP urinary antigen test. Ercis et al. (11) reported that this test revealed a sensitivity of 72.7% and a specificity of 97.6%. A renal biopsy was helpful in making the early diagnosis of HUS and in estimating the prognosis and therapy selection. Methylprednisolone pulse therapy followed by oral steroid in addition to antibiotic therapy was effective for early recovery.

The present patient could have had DIC in the beginning of the clinical course. DIC was initially considered according to the criteria for DIC (the presence of underlying disease and clinical symptoms, platelet count <50,000/μL, and marked increase of FDP) (9). However, the prothrombin time and her plasma fibrinogen level were normal. We consider that DIC contributed little to her renal failure, and that renal fibrinolysis as a response to HUS contributed to the increased FDP. ADAMTS13 activity determination is necessary in all patients identified as having aHUS, as manifestations of aHUS and thrombotic thrombocytopenic purpura (TTP) may overlap. ADAMTS13 activity <10% of normal is significant of TTP (2). TTP was excluded in the present patient, because ADAMTS13 deficiency was mild.

Although SP is a common pathogen in children and adults, SP-HUS usually occurs in children. Our review of the literature revealed that only 4 adult cases of SP-HUS have been reported (4-7). Table 1 summarizes clinical features of the 4 reported cases and the present case (1 male and 4 females). The mean age was 48 years (range 35 - 62). Two patients including the present patient had undergone splenectomy. Three patients developed SP bacteremia. The apparent source of bacteremia was not described in these cases. One other patient and the current patient presented with respiratory symptoms. Renal histological findings were observed only in the present patient. All patients were treated with antibiotics, and one other patient and the current patient were treated with steroids. Plasma exchange and hemodialysis were performed in 3 and 4 patients, respectively. Four patients recovered, but 1 patient underwent renal transplantation. Early recovery without hemodialysis was observed in the present patient after steroid pulse therapy. Previously reported cases and our case indicate that SP-HUS can rarely occur in both splenectomized adults and immunocompetent adults, and that plasma exchange and steroid therapy in addition to antibiotic therapy may be useful in patients with SP-HUS.

Neuraminidase produced by SP is thought to play a pivotal role in the development of SP-HUS (1, 12). This enzyme, by removing neuraminic acids from the cell membranes, exposes the Thomsen-Friedenreich (T)-antigen on the surface of erythrocytes, platelets, and glomerular endothelial cells, which is normally masked by neuraminic acid. Since the majority of people possess naturally occurring IgM antibodies to the T-antigen, exposure of the T-antigen results in antibody-mediated hemolysis, platelet aggregation, and glomerular endothelial damage. Theoretically, plasma exchange would successfully treat this condition by removing the circulating bacterial neuraminidase. In the recent guidelines for the management of aHUS, a trial of plasma exchange is suggested (13).
It has also been reported that systemic release of proinflammatory cytokines may be responsible for the coordination of acute inflammatory processes in some children with HUS (14). Because a systemic proinflammatory cytokine response was considered in the present patient, methylprednisolone pulse therapy was performed. This therapy was effective for early recovery of SP-HUS. Our review of the literature revealed that a similar child case has been described previously. Tsuruga et al. (15) reported a 5-year-old girl with typical HUS and central nervous system involvement. Because proinflammatory hypercytokinemia was strongly suspected in this case, anti-inflammatory cytokine therapy consisting of methylprednisolone pulse therapy and high-dose intravenous immunoglobulin was initiated. Following this therapy, a dramatic and rapid improvement of her clinical condition was observed.

Morel-Maroger et al. (16) examined clinicopathologic characteristics in 20 adult patients with HUS. They suggested that early renal biopsies may be helpful in predicting prognosis in HUS; arterial lesions were of greater prognostic importance than glomerular lesions. Matsumae et al. (17) also examined clinicopathologic characteristics in 28 adult patients with HUS. They stated that it was very difficult to predict the outcome of the disease based on the clinical findings alone, and thus a renal histological examination was considered to help in determining the long-term outcome. In their series, the presence of arteriolar fibrinoid necrosis and expansion of glomerular subendothelial lucent zone appeared to have a significant influence on the renal survival. An early renal biopsy was performed after platelet transfusion in the present patient. Platelet transfusion is not contra-indicated, when a procedure at a risk of being hemorrhagic is scheduled in a severely thrombocytopenic patient, although platelet transfusion might worsen the microangiopathic process (2). In the present case with early recovery, neither severe vascular lesions nor marked expansion of glomerular subendothelial lucent zone were observed. This supports the observations by Morel-Maroger et al. (16) and Matsumae et al. (17).

In summary, SP infection should be considered as a causative etiology in all splenectomized patients with aHUS. An early renal biopsy is helpful in predicting the prognosis and therapy selection. Steroid pulse therapy in addition to antibiotic therapy may be useful in patients with SP-HUS at an early stage of the disease.

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

Acknowledgement

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References


Table 1. Cases of SP-HUS in Adult Patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age</th>
<th>Sex</th>
<th>Underlying factor</th>
<th>SP infection</th>
<th>RB</th>
<th>Antibiotics/s</th>
<th>PE</th>
<th>HD</th>
<th>Renal outcome</th>
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<td>von Eyben et al.</td>
<td>35</td>
<td>M</td>
<td>Post-splenectomy</td>
<td>Sepsis</td>
<td>–</td>
<td>PC</td>
<td>–</td>
<td>–</td>
<td>Improved</td>
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<tr>
<td>Myers et al.</td>
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<td>None</td>
<td>Sepsis</td>
<td>–</td>
<td>ABPC+GM</td>
<td>+</td>
<td>RT</td>
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<td>CTRX</td>
<td>+</td>
<td>+</td>
<td>Improved</td>
</tr>
<tr>
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<td>+</td>
<td>CTRX</td>
<td>+</td>
<td>+</td>
<td>Improved</td>
</tr>
<tr>
<td>Present case</td>
<td>62</td>
<td>F</td>
<td>Post-splenectomy</td>
<td>URTI</td>
<td>+</td>
<td>MINO</td>
<td>–</td>
<td>–</td>
<td>Improved</td>
</tr>
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