Delayed Hemolytic Uremic Syndrome Presenting as Diffuse Alveolar Hemorrhage

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Hemolytic uremic syndrome (HUS) is defined by the triad of mechanical intravascular hemolytic anemia with schistocytosis, thrombocytopenia and acute renal failure. Pulmonary involvement in HUS is known to be rare. We present the case of a 25-year-old male with diffuse alveolar hemorrhage and myocarditis followed by atypical hemolytic uremic syndrome. In this case, successful treatments included steroid pulse therapy for the fatal alveolar hemorrhage and plasma exchange for the hemolytic uremic syndrome.

Key Words: hemolytic-uremic syndrome; hemorrhage; plasma exchange.

Diffuse alveolar hemorrhage (DAH) is a life threatening disorder with high mortality.[1] The treatment of alveolar hemorrhage varies according to the etiologies. The alveolar hemorrhage in hemolytic uremic syndrome (HUS) has been rarely reported as complication.[2-5] We report a case of atypical HUS which manifested with alveolar hemorrhage, respiratory failure and myocarditis even before thrombocytopenia and hemolytic anemia developed. We will discuss the causes and treatment of atypical alveolar hemorrhage in this case review.

CASE REPORT

A 25-year-old man was transferred to the emergency department with a 4-day history of fever, dyspnea and hemoptysis, despite having received high-dose corticosteroid therapy in a local tertiary hospital. The patient was a nonsmoker, and did not have any history of drug use, recent travel, tuberculosis exposure, or a significant past medical history.

On physical examination, his temperature was 38.0℃, his heart rate was 116 beats/min, and his blood pressure was 188/89 mmHg. His respiratory rate was 26 breaths/min. There were no signs of arthritis, skin rashes, or lymphadenopathy. He did not have any abdominal discomfort or diarrhea. Physical examination was unremarkable except for mild crackles over both lower lobes.

Initial laboratory findings showed a hemoglobin level of 14.4 g/dl, a white blood cell count of 15,000/µl (neutrophil count 83.7%), and a platelet count of 134,000/mm³. Chemical values were notable for a blood urea nitrogen of 32.2 mg/dl and a creatinine of 2.6 mg/dl (FeNa 7.6%). Urinalysis showed 1+ blood cells and 2+ proteins. The activated partial thromboplastin time and prothrombin time were in normal ranges. Blood gas analysis revealed a pH of 7.49, PaCO₂ 31 mmHg, PaO₂ 57 mmHg, HCO₃⁻ 23.6 mmol/L, and SaO₂ 92% while breathing room air. On reverse transcriptase-polymerase chain reaction (RT-PCR) testing for respiratory viruses, only rhinovirus was found. Immunological survey including antinuclear antibody, anti double stranded DNA antibody, antitiglomerular basement membrane antibody, antineutrophil cytoplasmic antibody were negative. The complement components were normal (C3 130 mg/dl, C4 38 mg/dl). R.tsutsugamushi antibody, leptospira antibody and Hantaan virus antibody on serologic tests were negative.

A chest roentgenogram showed bilateral alveolar infiltrates (Fig. 1a). Chest CT scans showed consolidation and edema with multifocal ground glass opacities (Fig. 1b). Echocardiography showed that left ventricular systolic function was reduced to 35%. Severe global hypokinesia of the left ventricle and my-
The patient was placed on IV moxifloxacin following cultures. On the second day after admission, intubation was performed due to aggravated hypoxic respiratory failure. The steroid pulse therapy was administered under the suspicion of vasculitis involving the kidney, pulmonary alveolar epithelium, and myocardium. On fiberoptic bronchoscopy, bronchoalveolar lavage (BAL) fluid obtained from the lateral basal segment of the right lower lobe showed a progressively bloody appearance (Fig. 1c). The bacterial, fungal and mycobacterial cultures were all negative. *Pneumocystis jiroveci*, influenza A, parainfluenza, respiratory syncytial virus, cytomegalovirus, and adenovirus were not detected by multiplex PCR. Cytologic examination of the BAL fluid was negative for malignancy. After the steroid pulse therapy for two days, the alveolar infiltrates on the chest roentgenogram completely resolved (Fig. 1d) and the patient was weaned off. However, the renal function deteriorated and the patient underwent a percutaneous renal biopsy to distinguish the underlying diseases. The renal biopsy demonstrated that the glomerular capillary loops showed fibrin thrombi with capillary congestion. On immunofluorescence, the glomerular sections reacted with antibodies specific for the heavy chains of IgG, IgA, and IgM, and against C3, C4, C1q, and fibrinogen (Fig. 2). On the basis of the renal biopsy results, he was diagnosed with an atypical hemolytic uremic syndrome complicated with alveolar hemorrhage and myocarditis.

On hospital day 7, the platelet count decreased steeply from 120,000/mm$^3$ to 59,000/mm$^3$, and schistocytes were observed on the peripheral blood smear. Following five days of once daily plasma exchange treatment, the patient showed a favorable re-
Fig. 2. Renal biopsy findings in hemolytic uremic syndrome. (A) Light microscopy showing congestion of glomerular capillary loops with fibrin thrombi (H & E stain; original magnification × 200). (B) Light microscopy showing renal arteriolar intimal thickening and narrowing of the lumen (H & E stain; original magnification × 400). (C) Acid fuchsin orange G staining showing focal fibrinoid deposits and thrombi in the glomerular capillary loops (AFOG × 200). (D) Immunofluorescence showing the glomerular localization of fibrinogen in the mesangium.

Fig. 3. Time course of hemoglobin, LDH (lactate dehydrogenase), platelet count, BUN (blood urea nitrogen) and creatinine levels during treatment. The period of plasma exchange is shown as the gray speckled zone.

response, with an increase in hemoglobin, a decrease in microangiopathic hemolysis, improvement of renal function and an elevation in platelet count to 141,000/µl. The EHEC (Entero-haemorrhagic Escherichia coli) toxin PCR was positive, but a stool culture was negative. The Positron Emission Tomography (PET) scan and bone marrow biopsy revealed no evidence of malignancy or other hematologic diseases. On transthoracic echocardiography, myocardial edema remained, but left ventricular systolic function improved to 53%. Fig. 3 shows longitudinal changes in the clinical markers according to treatment. We slowly tapered the steroid dose to 15 mg of oral prednisolone per day after three weeks. After 4 weeks, the patients was discharged in stable condition and followed up regularly.

DISCUSSION

HUS is classified as either diarrhea-associated/typical HUS or non-diarrhea/atypical HUS. Typical HUS making up 90 percent of all cases, is preceded by gastroenteritis with Shiga-toxin-producing bacteria, ranging from three days to more than two
weeks.[6] On the contrary, atypical HUS is associated with a variety of causes including dysregulation of the alternative complement pathway, autoimmune disorders, cancers, drugs (VEGF inhibitors such as bevacizumab), bone marrow transplantation, and infection.[7] The distinction of pathogenesis is blurred because Shiga toxin can also mediate alternative complement pathway activation and acquired complement dysfunction in typical HUS.[8]

In this case, no clinical symptoms of typical HUS were present except for the presence of EHEC toxin on PCR. In addition, the excellent response to plasma exchange raises the possibility of atypical HUS. Among the etiologies of atypical HUS, human immunodeficiency virus infection, malignancy, and immune-related diseases were excluded. The C3 and C4 levels were normal, but a complete genetic analysis for factor H, factor I, factor B, membrane cofactor protein (CD46) and ADMAMTS-13 could not be performed due to lack of utility. It is unclear whether Rhinovirus is an infectious trigger leading to atypical HUS along with impaired immune system. Several cases have shown that viruses may be a precipitating trigger in the pathogenesis of atypical HUS.[9] Influenza A causes hemolysis and erythrocyte fusion with viral neuraminidase, and produces anti-ADAMTS 13 autoantibodies. Vascular endothelium disruption by coxsackievirus and echovirus results in intravascular coagulation. It was reported that enterovirus may play a synergistic role in triggering HUS in VTEC (Verotoxin-producing E.coli) - positive HUS. Further research will investigate the connection between rhinovirus and endothelial injury leading to thrombotic microangiopathies.

The differential diagnosis of DAH includes small vessel vasculitis, immune complex-mediated vasculitis, toxic inhalation, bone marrow transplantation, infection and drug-associated disease.[10] The current hypothesis about alveolar hemorrhage in HUS is that endothelial damage, the landmark of thrombotic microangiopathy, results in alveolar wall necrosis, loss of capillary integrity and alveolar hemorrhage. The dramatic resolution of infiltration after corticosteroid therapy indicates that DAH may have been associated with destruction of the pulmonary vascular endothelium.

Cardiovascular dysfunction in patients with HUS tends to be underdiagnosed. The mechanisms leading to heart failure are due to volume overload after renal failure or myocardial microinfarctions caused by thrombi in the cardiac circulation.[11] Aggressive treatment including plasma exchange should be initiated immediately due to poor prognosis.

It is remarkable that renal insufficiency, alveolar hemorrhage, and myocarditis could be preceding manifestations prior to the development of typical features such as hemolytic anemia or thrombocytopenia. It accords with the previous report that alveolar hemorrhage and alveolar wall necrosis can occur even in the absence of fibrin thrombus deposition.[12]

In atypical HUS, plasmapheresis with infusions of fresh frozen plasma is the first treatment option.[13] Fortunately, our patient showed good response to fifth session of plasma exchange. The complement blocker, eculizumab (humanized monoclonal anti-C5 immunoglobulin G) should be considered for HUS patients who are resistant to plasma exchange.

In summary, this case highlights uncommon multivisceral complication of atypical HUS. Pulmonary hemorrhage associated HUS should be considered as an uncommon cause. Several investigations including infectious etiology or combined complement dysfunction are required. Kidney biopsy could contribute to distinguish the underlying atypical HUS from other collagen vascular diseases and to start appropriate treatment. Steroid therapy and plasma exchange should be performed in fatal hemorrhage and myocarditis in HUS.

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