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CASE REPORT

Pandemic H1N1 influenza A viral infection complicated by atypical hemolytic uremic syndrome and diffuse alveolar hemorrhage

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Abstract We report here on a case of a 27-year-old man with atypical hemolytic uremic syndrome and diffuse alveolar hemorrhage associated with influenza A H1N1 infection. Treatment with oseltamivir, plasma exchange and hemodiafiltration for the hemolytic uremic syndrome and meticulous supportive care with steroid pulse therapy for the pulmonary alveolar hemorrhage was successful in this case. We discuss the relationship between hemolytic uremic syndrome and influenza A and the underlying immunologic factors that should be tested in a patient with atypical hemolytic uremic syndrome. We also discuss using steroid therapy for patients with H1N1-related diffuse alveolar hemorrhage.

Keywords Atypical hemolytic uremic syndrome · Influenza A H1N1 subtype · Pulmonary alveolar hemorrhage · Oseltamivir · Plasma exchange

Introduction

Hemolytic uremic syndrome (HUS) is a rare disease in adults and accounts for <5% of the causes of acute renal injury. Compared to the common pediatric form, HUS in adults has more heterogenous causes and a worse prognosis. For pediatric cases, >80% of HUS is caused by *Escherichia coli* serotype O 157; H7 or shiga-like toxin. This usually responds well to plasma transfusion and supportive therapy. However, in adults, HUS comes from more heterogenous and complicated underlying diseases like HIV infection, cancer or organ transplantation [1]. Influenza A is a rare, but possible cause of de novo atypical HUS. Several recent pediatric cases reported that a novel swine-origin influenza A H1N1 strain triggered atypical HUS [2–7], but there have been no reported cases of H1N1-associated atypical HUS accompanied with pulmonary alveolar hemorrhage in adult patients.

We describe here a case of atypical HUS with pulmonary alveolar hemorrhage that was triggered by H1N1 and that was successfully treated with oseltamivir, plasma exchange and continuous hemodiafiltration therapy.

Case presentation

In December 2010, a previously healthy 27-year-old Korean man was transferred to our institute with a 5-day history of fever, malaise, nausea with vomiting, cough and blood-tinged sputum. Two days prior to admission, he visited a local clinic for progressive illness. Initial laboratory findings at the local clinic were hemoglobin level 13.0 g/dL, platelet count 30,000/μL, aspartate transaminase level 165 IU/L, blood urea nitrogen level 33.8 mg/dL, and creatinine level 3.2 mg/dL. A nasopharyngeal swab was positive for influenza A using the rapid antigen detection test. He was administered oseltamivir. Next day, he became oliguric and was transferred to our hospital. On admission, a physical examination demonstrated a body temperature of 38.3°C, a blood pressure of 120/70 mmHg, a pulse rate of 90/min, and a respiratory rate of 25/min. The initial

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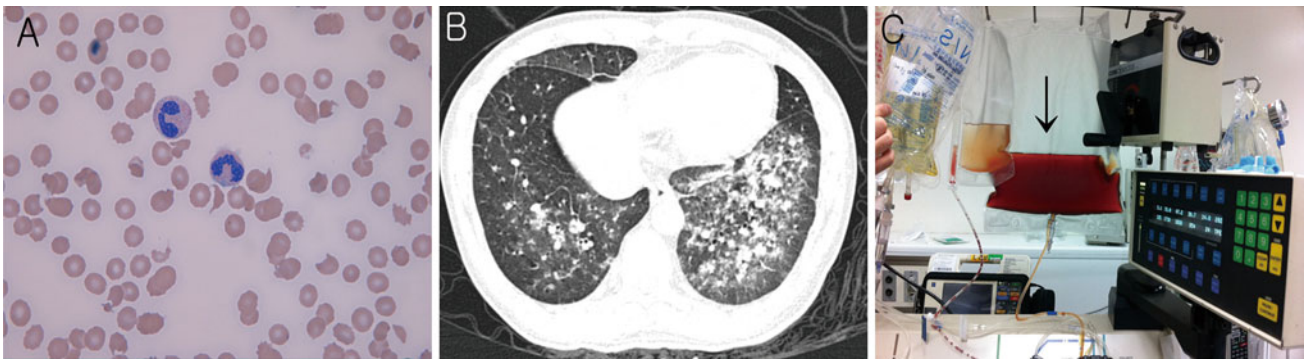

Fig. 1 Initial findings of the peripheral blood smear, chest computed tomography (CT) and plasma exchange. **a** The peripheral blood smear showed marked schistocytes (8–10/HPF × 1000). **b** Chest CT showed multiple ground glass opacities and consolidation on both lung fields. **c** The returned plasma from the patient (*arrow*) was *reddish*, which implied extensive hemolysis

laboratory data revealed microangiopathic hemolytic anemia [hemoglobin level: 11.1 g/dL, schistocytosis at 8–10/HPF (Fig. 1a), thrombocytopenia (platelet count 26,000/μL), lactate dehydrogenase >6,000 IU/L, aspartate transaminase >254 IU/L, total bilirubin/direct bilirubin 2.00/0.66 mg/dL, direct and indirect Coombs' test: negative], severe renal failure with a blood urea nitrogen level of 60.5 mg/dL and a creatinine level of 7.93 mg/dL. The serum sodium, potassium and chloride levels were 142.8, 4.12 and 114.7 mmol/L, respectively. His urine color was brown and urinalysis showed hematuria (urine RBCs 21–29/HPF) and proteinuria (protein 3+ with a urine SG of 1.015 and a urine protein/creatinine ratio of 2,521.57 mg/g). Mild pyuria was found (urine WBCs 3–5/HPF) but pathologic casts were not seen. The urinary indices such as the fractional excretion of sodium (FeNa) or the fractional excretion of urea (FeUrea) implied the acute kidney injury was intrinsic (FeNa 7.8%, FeUrea 36.2%). The prothrombin and partial thromboplastin times were within normal range. Immunologic investigations showed a decreased complement factor C3 level (69.9 mg/dL) with a normal C4 level (12.2 mg/dL). The antiglomerular basement membrane antibody and antineutrophil cytoplasmic antibody were negative. Atypical HUS was suspected and emergency plasma exchange was planned. During the preparation for plasma exchange, conventional hemodialysis was started; however, just after the start of hemodialysis, he developed massive hemoptysis. The oxygen saturation fell to 80% and the hemoglobin level declined to 6.8 g/dL. A chest X-ray showed bilateral diffuse alveolar infiltration. A computed tomography scan of the chest was performed and we noted multiple ground glass opacities and consolidation on both lung fields (Fig. 1b). Intubation and mechanical ventilation were started due to hypoxic respiratory failure and steroid pulse therapy with prophylactic ceftriaxone was started under the suspicion of diffuse alveolar hemorrhage. He was transferred to the intensive care unit (ICU) and conventional hemodialysis was replaced with continuous venovenous hemodiafiltration (CVVHDF). Plasma exchange was started 8 h after admission to the ICU. The returned plasma from the patient was reddish, which implied extensive hemolysis (Fig. 1c). Plasma exchange was started using one plasma volume.

On day 2, the local clinic reported that the polymerase chain reaction (PCR) for H1N1 was positive. Seventy five mg of oseltamivir was administered once daily for 10 days via a nasogastric tube in doses adjusted for the CVVHDF. The daily plasma exchange, CVVHDF and mechanical ventilation care were maintained. On day 4, his urine started to flow out and the chest X-ray began to clear up. The intravenous furosemide infusion was tapered until day 9 and the urine output increased to 2,500 ml/day. On day 13, the CVVHDF was discontinued; however, just after discontinuation of the CVVHDF, the serum creatinine rose from 2.68 to 5.89 mg/dL, but 3 days later, it had gradually decreased (Fig. 2). After 10 days of plasma exchange, the microangiopathic hemolytic anemia started to respond. A peripheral blood smear showed a decreased schistocyte count to 3−5/HPF. On day 17, the patient's platelet level rose to 101,000/μL, the lactate dehydrogenase level decreased to 546 IU/L and the schistocytes disappeared, and therefore the plasma exchange was stopped. However, his chest X-ray became worse and the hemoglobin level did not increase. His body temperature rose to 38.8°C and the laboratory data showed severe leukocytosis and the serum C-reactive protein level increased to 13.38 mg/dL. Repeated nasopharyngeal swab rapid antigen tests for influenza A were performed, but PCR test for H1N1 turned negative. A fiberoptic bronchoscopy was performed and revealed active bleeding on both lobes. Purulent and thick sputum was drained from the right upper lobe bronchus. Recurrent pulmonary alveolar hemorrhage and superimposed bacterial pneumonia were suspected. The antimicrobial agent was changed to vancomycin and ceftazidime and the

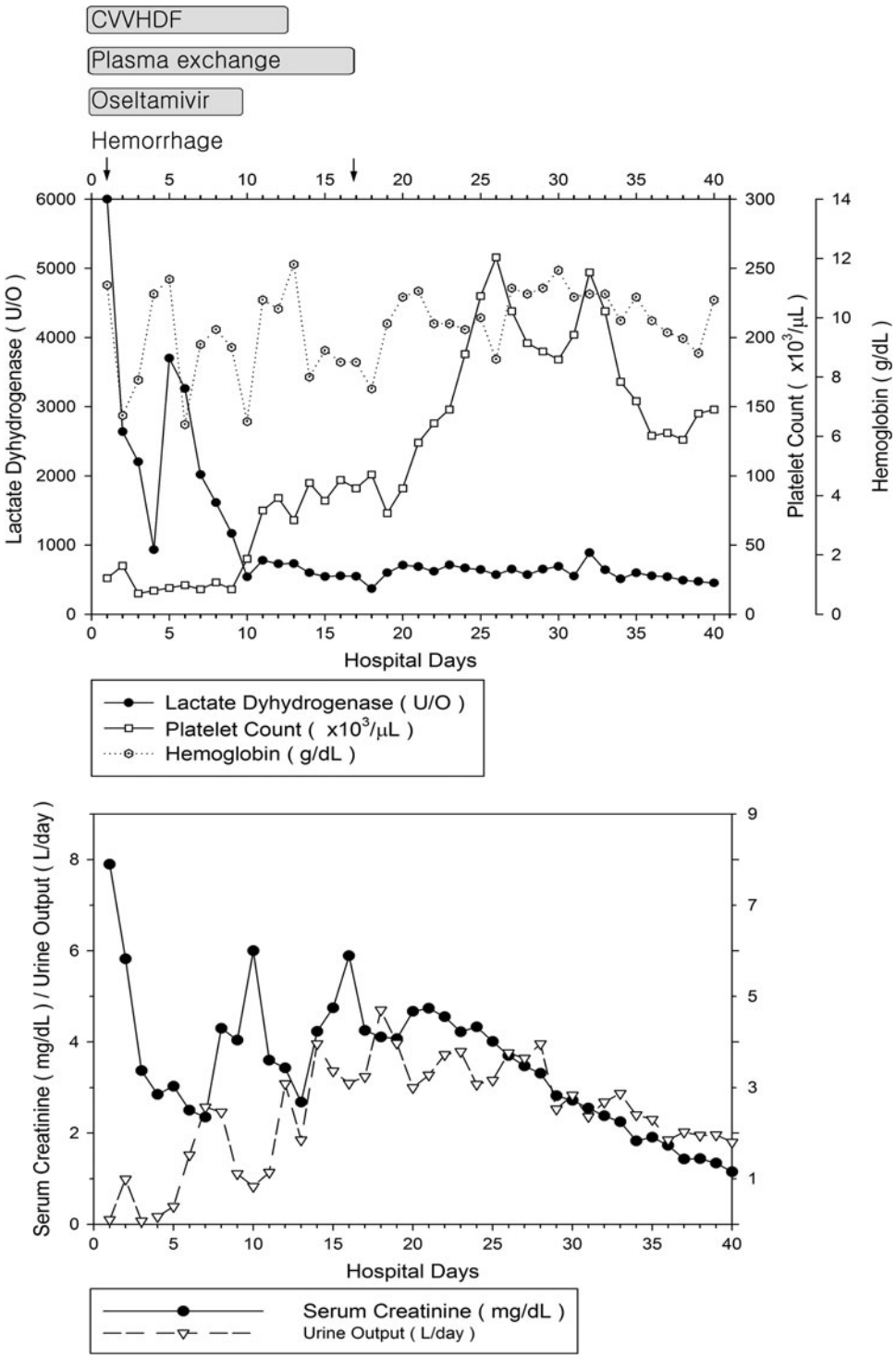

Fig. 2 Changes of clinical parameters and laboratory results throughout the follow-up period. *Gray boxes* represent the treatment duration and *black arrows* indicate the occurrences of pulmonary alveolar hemorrhage

patient was followed up with serial chest X-rays. The bilateral pulmonary infiltration soon disappeared, but the consolidation on the right upper lobe became worse. The microbiologic data from the bronchial washing fluid reported that methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant *Acinetobacter baumannii* (CRAB) were cultured. On day 18, the antibiotics were changed to linezolid, ampicillin/sulbactam and colistin. Fortunately, the antibiotics were effective; the fever subsided, the chest X-ray improved and the C-reactive protein fell to 1.34 mg/dL. On day 29, weaning the patient off mechanical ventilation was successful and extubation was performed the next day. On day 30, his hemoglobin was 10.8 g/dL, the platelet count was 247,000/

μL and the lactate dehydrogenase level returned to 549 IU/L. No more schistocytes were seen. His creatinine level fell to 1.14 mg/dL and the urine output was 80–90 ml/h without any diuretics. The atypical HUS associated with pandemic influenza A H1N1 and accompanying pulmonary alveolar hemorrhage complicated by MRSA and CRAB pneumonia were all resolved.

Discussion

Shiga and verotoxin-producing bacteria and *Streptococcus pneumoniae* are well known causative infectious etiologies of HUS [8]; however, there are few case reports on influenza A triggering HUS. In 1973, Symmer [9] reported on a case of thrombocytopenic purpura and hemolytic anemia after inoculation against influenza. In 1984, Claude et al. [10] first reported on a patient with HUS who was concurrently diagnosed with influenza A infection; by 2008, there were only 2 reported cases of HUS associated with influenza A [11, 12]. It is not clear whether the virulence of influenza A is important in causing HUS; however, after the emergence of a new strain of human influenza A (H1N1) virus in 2009, there have been more reports of H1N1 causing de novo HUS in children [2–7].

The mechanisms of influenza A H1N1 triggering HUS have not yet been defined, although some authors have suggested that viral neuraminidase plays a role in inducing HUS [4]. Because neuraminidase and hemagglutinin are major membrane glycoproteins found on the surface of influenza virus, and viral neuraminidase, which cleaves sialic acid residues from various glycoproteins on the surface of red blood cells, unmasks Thomsen–Friedenreich (TF) cryptantigen, this participates in hemolysis and renal failure [13].

The increased understanding of the molecular mechanisms has recently revealed disorders of complement regulation [14, 15] or ADAMTS13 deficiency [16], which play major roles in the pathogenesis of HUS. These etiologies are differentiated by the infectious etiology and are classified as atypical HUS [17]. Gain-of-function mutations or loss-of-function mutations in the genes encoding complement regulatory proteins activate the alternative complement pathway, and this causes endothelial damage in HUS. Complement factor H (CFH), factor I (CFI) and membrane cofactor protein (MCP or CD46) are related to loss-of-function mutations, which are seen in 60% of patients with atypical HUS, and complement factor B or C3 are related to a gain-of-function mutation [17]. The prognosis is completely different according to the gene mutation; mutation in the CD 46 gene alone is related to a good prognosis and mutations in the CFH or CFI gene are related to a poor prognosis. In both cases, however, if complement activation in HUS is confirmed, then specific drugs like eculizumab, a humanized monoclonal antibody that blocks C5 activation and prevents common terminal complement pathway activation, can be considered as an alternative therapy for the cases that are refractory to plasma exchange [7, 18].

Both an impaired immune system and a combined etiology with an infectious trigger can lead to atypical HUS. Taylor et al. [19] strongly recommended that in all patients presenting with clinical features compatible with a diagnosis of atypical HUS, the serum levels of C3, C4, factor H and factor I should be measured even if the infectious etiology was found, because the results guide the prognosis and treatment options. In our case, we tried to reveal the underlying immunologic impairment. The C3 and C4 levels were tested; the C3 level was low and complement dysregulation-related HUS was suspected. We could not check factor H, factor I and ADMAMTS-13 due to the lack of utilities. Since our case responded well to plasma exchange for both the renal and hematologic aspects, our case might have had impairment in the CD 46 gene locus.

In previously reported pediatric cases, some authors tried to reveal the underlying immune dysregulation, but only one case had underlying C3 gene mutation. Caltik et al. [5] reported on a 15-year-old female with atypical HUS that was triggered by H1N1 infection. They checked C3, C4, factor H, factor I and autoantibody to factor H, but no abnormality was found. Al-Akash et al. [7] reported on a 15-year-old female with recurrent attacks of atypical HUS. She had a C3 heterozygous gene mutation and was treated with eculizumab after the 8th session of plasma exchange.

We considered trying eculizumab if the patient did not respond to plasma exchange. Fortunately, our case recovered after the 16th session of plasma exchange, but eculizumab can be a good therapeutic option for cases of refractory HUS with abnormal complement activation.

The presentation of HUS in our case was more severe than that of the other reported pediatric cases and the H1N1 was also complicated with pulmonary alveolar hemorrhage. A previous autopsy study found that most cases of severe H1N1 viral infection had diffuse alveolar damage and 5 of the 20 patients had extensive hemorrhage with bronchiolar and alveolar epithelial cell damage [20]. Several cases of H1N1 pneumonia that were complicated with pulmonary alveolar hemorrhage have been reported. However, corticosteroid therapy is controversial for treating H1N1-associated alveolar hemorrhage [21–23]. We tried methylprednisolone 500 mg/day for 3 days because we thought that the pulmonary alveolar hemorrhage was associated with the destruction of the alveolar capillary membrane. Our patient had recurrent episodes of pulmonary alveolar hemorrhage on day 15, but we did not use

steroid therapy during the second episode of hemorrhage because of the combined bacterial pneumonia. The prolonged ventilation care resulted in MRSA and CRAB pneumonia, but early recognition of the pathogen by repeated bronchoscopy and adequate use of antimicrobial agents led to a favorable result.

Based upon this report, we want to share our experience with an adult case of H1N1 influenza A infection complicated by atypical HUS and diffuse alveolar hemorrhage. Even though it is rare, influenza A H1N1 should be considered as a causative etiology in patients with atypical HUS. If H1N1 is detected on a nasal swab, then oseltamivir should be administered and early plasma exchange with hemodialysis should be considered for cases of HUS. An infectious etiology alone can cause de novo HUS, but the presence of a combined immunologic defect in the complement activation pathway should be assessed because it is closely associated with the prognosis and treatment options.

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