Case Report

Life-Threatening Extrarenal Manifestations in an Infant with Atypical Hemolytic Uremic Syndrome Caused by a Complement 3-Gene Mutation

Sa Ra Han^{a, b} Myung Hyun Cho^a Jin Soo Moon^a Il Soo Ha^a
Hae Il Cheong^{a–c} Hee Gyung Kang^{a, b}

^aDepartment of Pediatrics, Seoul National University College of Medicine, Seoul, Republic of Korea; ^bDepartment of Pediatrics, Seoul National University Hospital, Seoul, Republic of Korea; ^cKidney Research Institute, Medical Research Center, Seoul National University College of Medicine, Seoul, Republic of Korea

Keywords

Atypical hemolytic uremic syndrome · Extrarenal manifestations · Gastrointestinal bleeding · Pulmonary hemorrhage · Eculizumab

Abstract

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment caused by uncontrolled activation of the complement system. About 20% of patients show extrarenal manifestations, with central nervous system involvement being the most frequent. We described the clinical course and management of aHUS in an infant, that was caused by a complement 3 (C3) gene mutation with severe extrarenal manifestations. **Case Presentation:** A 4-month-old girl visited our hospital for jaundice and petechiae. Laboratory tests revealed microangiopathic hemolytic anemia, thrombocytopenia, and hyperazotemia. She was diagnosed with aHUS with a C3 p.E1160K mutation. Daily fresh-frozen plasma (FFP) therapy was administered; however, she experienced the severe extrarenal manifestations of pulmonary hemorrhage and gastrointestinal bleeding. With aggressive treatment, supportive care, and daily FFP transfusion, the patient recovered and was discharged after 72 days of hospital stay, on a regular FFP transfusion. Four months after diagnosis, she was switched to eculizumab treatment. Twenty months have passed since then and she has been relapse-free until now. **Conclusion:** aHUS is rare but has a devastating course if not properly treated. Se-

Sa Ra Han and Myung Hyun Cho contributed equally to this work.

Hee Gyung Kang, MD, PhD
Department of Pediatrics, Seoul National University Children's Hospital
101 Daehak-ro, Jongno-gu
Seoul, 03080 (Republic of Korea)
E-Mail kanghg@snu.ac.kr

vere extrarenal manifestations, such as pulmonary hemorrhage and gastrointestinal bleeding, can develop in aHUS caused by a C3 mutation. In our case, long-term management with eculizumab resulted in relapse-free survival.

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Introduction

Hemolytic uremic syndrome (HUS) is a type of thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. HUS typically occurs as a complication of enterohemorrhagic *Escherichia coli* infection, usually in children. Although a typical HUS may be life-threatening, it is usually self-limited with conservative management [1]. Atypical HUS (aHUS), a very rare disease, usually occurs without prodromal bloody diarrhea [1]. Presentation at a very young age strongly suggests aHUS rather than Shiga toxin-related HUS. Most aHUS is now known to be caused by uncontrolled activation of the complement system. Many components of the complement system and their regulators have been found to be associated with aHUS when aberrant, such as complement factor H (CFH), factor I, and complement 3 (C3) [1]. However, in <1% of thrombotic microangiopathy cases, especially in infants <1 year of age, cobalamin-C deficiency plays a causative role [2].

The most common cause of aHUS is a CFH defect, from mutation of the gene or an interfering antibody. The natural course is relatively well known; patients with a CFH mutation often suffer from multiple recurrence of aHUS, which would be detrimental to renal function [1]. Management of aHUS caused by CFH mutation includes massive plasma therapy, liver transplantation, and, currently, eculizumab administration (anti-C5 antibody) [1]. On the other hand, the clinical course of aHUS associated with other components of the complement system is not as well known, due to the rarity of aHUS. Heterozygous C3 mutations account for about 4–10% of patients [1]. C3 gene mutations are associated with poor outcomes. Only 40–50% of the patients experience remission and about 60% progress to end-stage renal disease or death [1].

The renal manifestation of aHUS is a required symptom for diagnosis. However, aHUS can also be associated with severe extrarenal manifestations. Although aHUS is known to involve mainly the renal vasculature, other systemic vascular structures can be involved. About 20% of patients show extrarenal manifestations, with central nervous system (CNS) involvement being the most frequent [3]. Gastrointestinal bleeding and pulmonary hemorrhage are observed infrequently [4].

Here, we describe the clinical course and management of an infant patient with aHUS caused by a C3 mutation with severe extrarenal manifestations.

Case Presentation

A 4-month-old girl visited our hospital for jaundice and petechiae. She had briefly had fever 4 days prior to admission, but this had subsided spontaneously. Her skin color became yellow and petechiae appeared over her whole body. Her urine became dark red and the output diminished. Anemia and hyperazotemia were diagnosed at a local hospital, and she was then transferred to our hospital. Her past medical history and family history were unremarkable.

Physical examination revealed anemic conjunctiva, icteric sclera and skin, and petechial rash on both arms and the abdomen. Her vital signs were as follows: blood pressure, 114/53 mm Hg; heart rate, 132 beats/min; respiratory rate, 40 breaths/min; body temperature,

Fig. 1. **A** Patient's hemoglobin, platelet trend, and estimated glomerular filtration rate (eGFR), urine protein/creatinine ratio trend during continuous renal replacement therapy (CRRT), hemodialysis, fresh-frozen plasma (FFP) infusion, and eculizumab treatment. Black arrows, red blood cell transfusion; gray arrows, hemodialysis. **B** Esophagogastroscopy shows diffuse esophageal bleeding. **C** Biopsy demonstrates diffuse fibrinoid necrotic tissue and acanthotic squamous epithelium.

36.7°C. Results of neurological and abdominal examination were unremarkable. Initial blood test results were as follows: white blood cell count, 20,010/ μ L; hemoglobin level, 5.8 g/dL; platelet count, 97,000/ μ L (Fig. 1A); reticulocytes, 10.9%; blood urea nitrogen, 68 mg/dL; creatinine, 0.84 mg/dL; lactate dehydrogenase, 1,548 IU/L; negative Coombs test; fragmented red blood cells on peripheral blood smear; normal coagulation panel. A low C3 level of 52 mg/dL (normal range: 70–150 mg/dL), a complement 4 level of 18 mg/dL (normal range: 10–35 mg/dL), and a negative stool enterohemorrhagic *E. coli* PCR were observed. Urinalysis showed blood 3+ and protein 4+. Tests for viral infections were all negative. Under suspicion of aHUS or thrombotic thrombocytopenic purpura, she was treated with a daily fresh-frozen plasma (FFP) transfusion; later, ADAMTS13 activity was found to be at 83% and a heterozygous mutation c.3478G>A in exon 27 [p.Glu(GAG)1160Lys(AAG)] of C3 was identified using Sanger sequencing. She was diagnosed with aHUS with a C3 mutation. Genetic testing revealed that her sibling had the same mutation, but had not presented any manifestations of aHUS up to the age of 9 years.

Despite FFP transfusion (20 cm³/kg) for 4 consecutive days, hemolysis persisted, her creatinine levels were raised, and her urine output decreased. Volume overload was refractory, so on day 5 after admission, hemodialysis was initiated and plasmapheresis with FFP was performed for the next 10 days. Her blood urea nitrogen and creatinine levels continued to increase, up to 54 and 1.61 mg/dL, respectively (Fig. 1A). On day 19, she showed signs of respiratory difficulty. A chest plain radiograph revealed pulmonary edema and right pleural effusion. On intubation, fresh blood was visible in the upper airway and her heart rate dropped to 80 beats/min. After 6 min of cardiac massage her heart rate recovered. She was transferred to a pediatric intensive care unit and both daily FFP transfusion and continuous renal replacement therapy (CRRT) were performed. In 2 days, the patient's platelet count began to rise to >100,000 /μL. However, on day 28, fresh blood was drained via a Levin tube and her hemoglobin levels dropped. Diffuse bleeding and mucosa dissociation from the esophagus were observed on endoscopy (Fig. 1B). A biopsy showed diffuse fibrinoid necrotic tissue and an acanthotic squamous epithelium (Fig. 1C). Suspecting an extrarenal manifestation of aHUS or toxic epidermal necrolysis (TEN), CRRT with a daily FFP transfusion was continued, and empirical immunoglobulin was administered along with a proton pump inhibitor and sucralfate. Three days later, the bleeding subsided, and the patient was transferred to the general ward of the hospital on day 38. She was discharged on day 72, without any further events, on regular FFP transfusion. The final laboratory results before discharge were as follows: platelet count 266,000 /μL, hemoglobin 10.7 g/dL, lactate dehydrogenase 436 IU/L, C3 complement level 75 mg/dL, and creatinine 0.43 mg/dL (Fig. 1A).

In the outpatient clinic, she received FFP transfusion twice a week. Four months after diagnosis, she was switched to eculizumab treatment. This medication has been administered until now. Her platelet count was >200,000 /μL, creatinine 0.28 mg/dL, lactate dehydrogenase 300 IU/L, and C3 >60 mg/dL at the last follow-up at 2 years after diagnosis.

Discussion

We report a pediatric case of *C3* mutation-associated aHUS with the severe extrarenal manifestations of pulmonary hemorrhage and gastrointestinal bleeding. In our case, a previously reported c.3478G>A (p.E1160K) mutation in exon 27 of *C3* was identified; this site is located in the binding site for CFH, thus resulting in a decreased binding affinity and persistently activated C3b, as with most *C3* mutations associated with aHUS [5, 6]. In a study on 2 aHUS cohorts, 14 patients with *C3* mutations were found and half of these did not recover their renal function after their initial presentation. Twelve of the 14 patients later received kidney transplantations and 5 of these (42%) experienced recurrence [6]. Our patient fortunately recovered from her life-threatening renal and extrarenal manifestations of aHUS with aggressive plasma therapy. Currently, she has been followed-up for approximately 2 years, and no renal or extrarenal recurrences have been observed with long-term eculizumab treatment.

The extrarenal manifestations were life-threatening in our case, with massive gastrointestinal bleeding and pulmonary hemorrhage. Fremeaux-Bacchi et al. [4] reported only 2 cases of pulmonary hemorrhage among 89 aHUS pediatric patients and Fidan et al. [7] reported only 5 cases of gastrointestinal bleeding among 169 pediatric aHUS patients. In patients with *C3* mutations, CNS, gastrointestinal, and cardiovascular involvement have been reported [7]. In view of the fact that C3 is present in the plasma, we tried to manage our patient with massive plasma therapy, but severe bleeding and esophageal denudation occurred. Gross endoscopic findings of her esophagus were similar to TEN, but skin detachment (a pathognomonic sign of TEN [8]) was not observed. To our knowledge, there have been no

reports of TEN as an extrarenal manifestation of aHUS. Gastrointestinal vascular involvement of aHUS would explain the esophageal denudation of this patient.

The efficacy of eculizumab on *C3* mutation-associated aHUS was reported previously [1]. Since eculizumab can be a life-saving treatment, we had wanted to treat our patient with this medication at diagnosis; however, this was not possible due to its exorbitant price. She could receive eculizumab only after obtaining financial support from a patient-support foundation a few months after the diagnosis. Although she showed clinical improvement before eculizumab was administered, we reckoned that this drug was needed to avoid life-threatening recurrences and improve her renal function. While aHUS associated with *C3* gene mutation has a high rate of recurrence [9], at the time of writing, our patient has been in clinical and biochemical remission with eculizumab for 2 years. Eculizumab may have prevented disease recurrence in our case. In addition, after eculizumab administration, her quality of life improved as well as her renal function (Fig. 1A). The patient used to visit our clinic twice a week for FFP transfusion, but on eculizumab she now visits twice a month only.

Discontinuation of eculizumab leads occasionally to relapse [10] and questions concerning the duration of eculizumab treatment are unanswered as of yet. While some patients are able to be successfully weaned off eculizumab [11], in some cases, discontinuation is associated with recurrence. Studies on the duration of treatment, long-term adverse effects, maintenance dose, and life-long maintenance treatment for these patients are still underway.

In conclusion, due to the rarity of aHUS, only a few data and clinical experiences were available until now. However, considering the devastating course of the disease if not properly treated, clinicians should never be reluctant to suspect aHUS and commence aggressive treatment when clinical findings suggest this rare disease. Severe extrarenal manifestations, like the pulmonary hemorrhage and gastrointestinal bleeding in our case, can develop during the course of the disease. Eculizumab was an excellent choice of treatment for *C3* mutation-associated aHUS.

Statement of Ethics

Institutional review board (No. H-0812-002-264) approval and written informed consent were obtained.

Disclosure Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Conceptualization: Kang H.G., Cheong H.I., Ha I.S., Moon J.S. Writing – original draft: Han S.R., Cho M.H.

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