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Single Case

O80:H2-Associated Hemolytic Uremic Syndrome without Hemorrhagic Colitis: A Case Report

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Keywords

Hemolytic uremic syndrome · Shiga toxin-producing *Escherichia coli* · O80:H2 · Hemorrhagic colitis · Case report

Abstract

Introduction: Hemolytic uremic syndrome (HUS) is characterized by progressive kidney injury accompanied by thrombotic microangiopathy, which is clinically defined as microangiopathic hemolytic anemia with thrombocytopenia and organ injury. Shiga toxin-producing *Escherichia coli* (STEC)-HUS is caused by infection with pathogenic *E. coli* strains, typically O157, O26, and O111. However, the prevalence of other types of pathogenic *E. coli* has been increasing, and these pathogens sometimes cause atypical clinical manifestations of STEC-HUS. ***Case Presentation:*** We report the case of a 3-year-old girl diagnosed with STEC-HUS associated with a rare O80:H2 stx2 serotype, characterized by an atypical clinical course. She presented with severe hemolytic anemia and mild renal dysfunction but did not have enterohemorrhagic diarrhea. The first culture test of her stool sample collected using a swab upon admission yielded no signs of STEC, leading to an initial diagnosis of atypical HUS; thus, eculizumab was administered adding to red blood cell transfusion and recombinant thrombomodulin alfa and haptoglobin. However, a subsequent culture test of her second stool sample revealed the presence of O80:H2 stx2, confirming the diagnosis of STEC-HUS. Subsequently, the patient's condition improved, and her serum creatinine level gradually normalized over the course of 3 months. ***Conclusion:*** Diligently diagnosis is crucial in cases lacking typical STEC-HUS symptoms. We advocate for repeated stool culture testing to ensure accurate identification and timely management of such cases.

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Introduction

Thrombotic microangiopathy (TMA) is clinically defined as microangiopathic hemolytic anemia with thrombocytopenia and organ injury [1]. Primary TMA includes two types of disorders: hereditary disorders caused by a single gene mutation and acquired disorders caused by secondary factors, such as toxins, drugs, and immunological dysfunction [1]. Hemolytic uremic syndrome (HUS) is one type of TMA that is characterized by the presence of progressive kidney injury [1]. Typical HUS is caused by Shiga toxin-producing *Escherichia coli* (STEC) infection, whereas atypical HUS is caused by the malfunction of complement-related genes. It is often difficult to differentiate between diagnoses at the onset of HUS. Nevertheless, the treatment strategies and prognoses for typical and atypical HUS cases differ; therefore, a prompt and accurate diagnosis is important. Symptoms and clinical course can be clues used to differentiate the diagnosis; however, the key to the diagnosis is proof of the STEC infection using culture tests of stool samples. Several types of pathogenic *E. coli* are causative bacteria. O157, O26, and O111 are well-known pathogenic *E. coli* strains that cause typical HUS [2]. Identification tests that allow a rapid diagnosis of these three types of pathogenic *E. coli* are available. However, when other types of *E. coli* are present, whether they produce Shiga toxin must be identified first; then, the type of *E. coli* must be determined at a specialized facility. Importantly, other types of *E. coli* sometimes induce atypical clinical manifestations of STEC-HUS; thus, accurate identification is required. Here, we report a case of STEC-HUS with an atypical course that was caused by pathogenic *E. coli* strain O80. The CARE checklist has been completed by the authors for this case report, attached as online supplementary material (for online suppl. material, see https://doi.org/10.1159/000539403).

Case Report

A 3-year-old girl with no notable medical history was admitted to our hospital due to severe anemia and thrombocytopenia. She presented with a 5-day history of vomiting, a single episode of loose stools 2 days prior to admission, and a low-grade fever 1 day before hospitalization, without any medication. She had exhibited no hemorrhagic diarrhea. None of her other family members experienced similar symptoms with her. On admission, her consciousness level was unimpaired; however, pallor was evident. Importantly, she did not have diarrhea. Her vital signs were as follows: body temperature, 38.1°C; respiratory rate, 22 breaths per minute; SpO_2, 99%; blood pressure, 94/44 mm Hg; and mildly elevated heart rate (144 beats per minute). Physical examination revealed only pale conjunctiva. Hematological findings indicated an elevated peripheral leukocyte count of 15,000/mm^3, hematocrit level of 13.5%, red blood cell (RBC) count of 1,570,000/mm^3, hemoglobin concentration of 4.6 g/dL, platelet (Plt) count of 29,000/mm^3, and the presence of fragmented RBCs. Laboratory serological test results revealed the following: elevated lactate dehydrogenase (LDH), 2,101 IU/L; total protein, 5.3 g/dL; albumin, 3.3 g/dL; creatinine, 0.71 mg/dL; urea nitrogen, 10.6 mg/dL; and potassium, 4.4 mEq/L. Additionally, haptoglobin was notably low at 8 mg/dL. Coagulation test results indicated fibrin and fibrinogen degradation levels of 239 mg/dL and a D-dimer level of 3.20 μg/mL. Urinalysis detected significant proteinuria (8.18 g/day), hematuria, and an elevated β2 microglobulin level of 8,178 μg/L. Serum immunoglobulin (Ig) levels (IgG, IgA, IgM) were within the normal range, as were the complement levels (Table 1). Based on these clinical and laboratory findings, we diagnosed her condition as TMA and suspected atypical HUS. Subsequently, we began RBC transfusion and administered recombinant thrombomodulin alfa and haptoglobin. By day 3 of admission, the culture test of the stool sample collected via swabbing showed no pathogenic *E. coli*. Moreover, assessments

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Table 1. Laboratory data at the time of admission

Urinalysis	
pH	7.0
Gravity	1.025
Protein	3+
Occult blood	3+
Glucose	–
Ketones	2+
RBC (/HPF)	30–49
WBC (/HPF)	1–4
Hyaline cast (/WF)	10–19
Epithelial cast (/WF)	20–29
TP/Cre, g/gCre	8.18
NAG, U/L	34.0
B2MG, μg/mL	8,178

Complete blood count	
WBC, /μL	15,000
RBC, /μL	1,570,000
Hb, g/dL	4.6
Hct, %	13.5
Plt, /μL	29,000
Fragment RBC	(+)

Coagulation	
PT, %	100.0
APTT, sec	23.9
Fibrinogen, mg/dL	239
FDP, μg/mL	2.5
D-dimer, μg/mL	3.20
vWF, %	134
ADAMTS13 activity	w.n.l

Biochemistry	
TP, g/dL	5.3
Alb, g/dL	3.3
BUN, mg/dL	41.0
Cre, mg/dL	0.71
CysC, mg/dL	1.33
UA, mg/dL	10.6

Biochemistry	
Na, mEq/L	139
K, mEq/L	4.4
Cl, mEq/L	101
Ca, mg/dL	8.8
P, mg/dL	4.7
LDH, IU/L	2,101
AST, IU/L	64
ALT, IU/L	15
T.Bil, mg/dL	1.6
CK, mg/dL	877
Glucose, mg/dL	94
CRP, mg/dL	0.08
Haptoglobin, mg/dL	8
IgG, mg/dL	682
IgA, mg/dL	59
IgM, mg/dL	77
C3, mg/dL	93
C4, mg/dL	20
ASO (titer)	≤10

Abs	
Anti-ADAMTS13 Ab	–
ANA	–
Anti-DNA Ab	–

Alb, albumin; Ab, antibody; ALT, alanine transaminase; ANA, antinuclear antibody; APTT, activated partial thromboplastin time; ASO, antistreptolysin O; AST, aspartate aminotransferase; B2MG, beta-2 microglobulin; BUN, blood urea nitrogen; C3, complement component 3; C4, complement component 4; Ca, calcium; CK, creatine kinase; Cl, chloride; Cre, creatinine; CRP, C-reactive protein; CysC, cystatin C; FDP, fibrin degradation product; Hb, hemoglobin; Hct, hematocrit; Ig, immunoglobulin; K, potassium; LDH, lactate dehydrogenase; Na, sodium; NAG, N-acetyl-beta-D-glucosaminidase; P, phosphorus; Plt, platelets; PT, prothrombin time; RBC, red blood cell; T.Bil, total bilirubin; TP, total protein; UA, uric acid; vWF, von Willebrand factor; WBC, white blood cell; w.n.l., within normal limits.

of von Willebrand factor, ADAMTS13 activity, and ADAMTS13 inhibitor yielded normal results. Negative results were observed for autoimmune antibodies (Abs), including anti-dsDNA IgG Abs, anti-Sm, anti-RNP, PR3-ANCA, MPO-ANCA, and anti-SS-A. Consequently, a diagnosis of atypical HUS was established, and treatment with eculizumab (ECU) commenced on day 4 of admission following the administration of the meningococcal vaccine and the initiation of intravenous ceftriaxone for prophylaxis. ECU administration resulted in an increased Plt count and decreased LDH level; however, improvement of the laboratory test results remained constrained, particularly with regard to renal dysfunction. Blood pressure peaked at 112/56 mm Hg but spontaneously improved and stabilized in the range of 90 s/50 s mm Hg. On day 8, the culture test of the stool sample collected on day 2 revealed a positive result for stx2. To further characterize the strain of *E. coli*, we sought the expertise of the National Institute of Infectious Diseases. Because of persistent kidney dysfunction despite improvements in the Plt count and LDH value (Fig. 1), a second infusion of ECU was administered on day 11, with parental consent. The next day, a fecal diagnostic test confirmed the *E. coli* serotype as O80:H2. The serodiagnosis of the *E. coli* infection corroborated the O80 infection, with a serum Ab titer of 1:320. An examination performed to determine the differential diagnosis of atypical HUS revealed negative results, including negative hemolysis test results, absence of anti-complement factor H Abs, and unremarkable results of a gene analysis to determine atypical HUS mutations. Thus, we made a definitive diagnosis of STEC-HUS. We discontinued administrating ECU. Subsequently, the patient's overall condition improved and she showed no significant adverse events except serum complement component 3 decrease due to ECU administration. She was discharged from the hospital on day 14. Over the course of 3 months, her serum creatinine level gradually normalized.

Discussion

Our case involved a 3-year-old girl with STEC-HUS associated with a rare pathogenic *E. coli* O80:H2 stx2 serotype characterized by an atypical clinical course without typical symptoms. The accurate identification of the *E. coli* serotype plays a pivotal role in the diagnosis of STEC-HUS. Pathogenic *E. coli* serotypes such as O157, O26, and O111 have been implicated in STEC-HUS cases [3–5]. However, the background of *E. coli* serotypes isolated from the stool samples of patients with STEC has evolved over the past decade. Surveillance reports from the National Institute of Infectious Diseases in Japan have highlighted this transformation [6]. In 2011, pathogenic *E. coli* strains recovered from enterohemorrhagic *E. coli* (EHEC) infections predominantly comprised O157 (75%) and O26 (11%), with O157, O26, and O111 collectively accounting for 90% of cases. However, by 2021, the prevalence of O157 decreased to 55.8%, and that of O26 decreased to 10.4%, whereas other serotypes emerged in diverse proportions (O103, 4.0%; O111, 2.8%; O145, 2.1%; and O128, 3.8%). The evolving serotype conditions pose challenges to the accurate diagnosis of HUS. Consequently, determining the specific *E. coli* serotypes present in STEC-HUS has become increasingly critical. Therefore, clinicians should pursue a comprehensive differential diagnosis of atypical HUS to ensure timely and precise management. We initially suspected the patient to have atypical HUS because of the absence of hemorrhagic diarrhea; however, the second stool culture revealed the rare subtype, O80:H2. Repeated stool culture could lead us to an accurate diagnosis. Therefore, we advocate for repeated stool culture testing when patients exhibit an atypical clinical course, concurrently with performing the test for diagnosis of atypical HUS including genetic tests.

In Japan, O80 has been identified as the pathogenic EHEC bacterium in only 7 cases, including ours, and 3 cases involved STEC-HUS. O80 is an extremely rare pathogenic *E. coli* strain in

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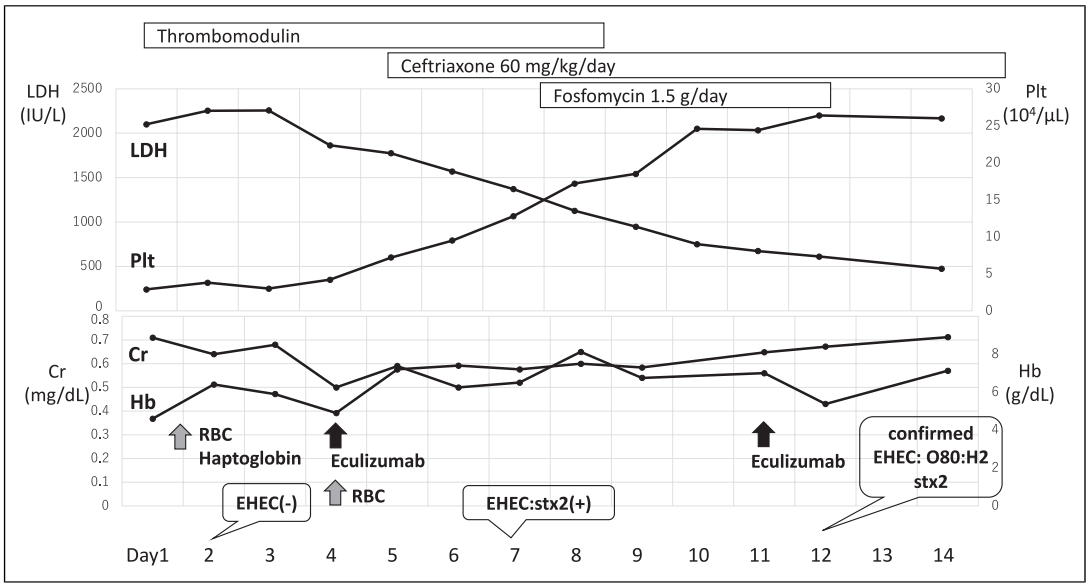

Fig. 1. Clinical course. Changes in significant laboratory data, examination results, and major therapies administered. Cre, creatinine; EHEC, enterohemorrhagic *Escherichia coli*; Hb, hemoglobin; LDH, lactate dehydrogenase; Plt, platelets; RBC, red blood cell.

Japan. However, in certain regions of Europe, O80 comprises a large portion of EHEC infections. Its emergence can be traced back to 2005, mainly in France, where 54 patients developed O80-associated EHEC infections between 2005 and 2014 [7]. It was limited to eastern France until 2014; however, it spread to all regions of France in 2016 [8]. Additionally, O80 was detected in 43 patients who presented with gastrointestinal symptoms or bloody stools in England and Scotland between 2013 and 2020 [3]. Although O80 has been detected in specific areas, it is possible that the coronavirus disease 2019 pandemic, which restricted people from traveling to other countries, may have temporarily constrained the global spread of new bacterial serotypes. Thus, an increase in O80 infections in Japan and other countries could occur in the future.

The incidence of STEC-HUS associated with O80 infection ranges from 25 to 92% [3, 7]. O80-associated STEC-HUS is associated with severe hemolytic anemia, mild or no bloody stools, and mild renal dysfunction [8]. The differences in the clinical characteristics between *E. coli* O157 and O80 are shown in online supplementary Table S1. Our patient experienced remarkable anemia and mild renal dysfunction, but no bloody stools, consistent with previously reported cases, and her renal dysfunction recovered in about 3 months. While a statistical analysis of the prognosis of O80-associated STEC-HUS is yet to be reported, the majority of documented cases indicate a favorable outcome. Nevertheless, a notable case involving a 16-month-old boy with O80-associated STEC-HUS was documented in the Netherlands. He exhibited non-bloody diarrhea for over 1 week, and coughing and vomiting for 2 days; subsequently, he developed convulsions and impaired consciousness before succumbing to multiple organ failure, including renal dysfunction and liver failure, attributable to TMA [9]. Therefore, the possibility of critical status development during treatment should be considered.

Regardless of the type of pathogenic *E. coli*, whether O157 or O80, treatment for STEC-HUS typically involves fluid infusion, blood transfusion, and other supportive treatments according to symptoms. Thrombomodulin alfa is a human protein that acts by inhibiting thrombin and stimulating protein C activities. It may be effective in treating thromboembolism and blood clotting disorders. There is a report suggesting a positive effect on TMA

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following hematopoietic stem cell transplantation [10]. Therefore, although evidence supporting the effectiveness of recombinant thrombomodulin for typical HUS is lacking, we administered thrombomodulin alfa due to our belief in its potential to improve TMA.

ECU is a recombinant monoclonal Ab that targets the complement protein C5 at the terminal of the classic complement pathway and is effective against atypical HUS. Regarding our case, we administered ECU because we assumed that atypical HUS had developed. After ECU administration, the results of her laboratory tests gradually improved; however, it was ineffective for renal dysfunction. Based on the pathogenic mechanisms of STEC-HUS, many researchers have expected that ECU could be a cure for severe STEC-HUS cases. The stx2 gene activates the complement pathway through an alternative pathway, induces P-secretin expression, and reduces CD59 [11]. In fact, patients with STEC-HUS have increased complement component 3 and C5b levels and decreased MCP levels [12]. Clinical improvement of STEC-HUS was first observed in 3 patients with severe STEC-HUS in Germany in 2011 [13]. Since then, some studies have suggested that ECU has a positive effect on STEC-HUS; however, the treatment was administered to only a small number of patients. Negative results have been reported as well because ECU was not as effective as plasma exchange and its positive effect was limited [14]. Therefore, the effectiveness of ECU for STEC-HUS remains controversial [11]. In our case, we administered ECU with parental consent, and some of the patient's laboratory data improved following ECU administration; however, renal dysfunction persisted. We speculated that renal dysfunction resulting from pathogenic *E. coli* infection is attributed not only to the activation of the secondary complement pathway by Stx but also to direct damage by Stx to the glomeruli and renal tubules [2]. A randomized controlled trial performed in France proved the efficacy of ECU for reducing renal sequelae within 1 year of onset, although the required renal replacement therapy within 48 h of onset did not significantly differ [15]. Because the number of studies is limited, more data, including data regarding other involved organs, are required before conclusions can be determined.

STEC-HUS is sometimes difficult to distinguish from atypical HUS and promptly diagnose, especially when the pathogenic *E. coli* strain is rare and patients do not present with typical symptoms. This atypical course of STEC-HUS emphasizes the importance of diligently diagnosing cases through repeated culture tests using sufficient stool samples and prompt treatment.

Statement of Ethics

Ethical approval was not required for this study, which was performed in accordance with national guidelines. Written informed consent was obtained from the parents of the patient for all the treatments the patients received and for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors, Sawako Yoshida, Eriko Tanaka, Zentaro Kiuchi, Saaya Nunokawa, Ayumi Kawahara, and Masami Narita, contributed to treating the patient. Sunao Iyoda contributed to identifying the type of the pathogen. Sawako Yoshida, Eriko Tanaka, and Zentaro Kiuchi contributed to writing and reviewing the manuscript.

Data Availability Statement

All data generated or analyzed are included in this article and its online supplementary materials. Further inquiries can be directed to the corresponding author.

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