Hemolytic Uremic Syndrome: An Increasingly Recognized Public Health Problem

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ABSTRACT: A 28-year-old man was referred and admitted to our hospital due to *Escherichia coli* O157–mediated hemorrhagic colitis with severe thrombocytopenia. A systemic workup concluded that the patient had acute pancreatitis as well as hemolytic uremic syndrome. The patient was ultimately discharged, with his platelet count having recovered. Our case serves an illustrative example of potentially serious complications of an increasingly recognized public health problem. Systemic studies on this topic are insufficient, and we strongly recommend the further accumulation of more experiences like ours. Several diagnostic and management concerns that emerged in this case are also discussed.

KEYWORDS: thrombocytopenia, hemolytic uremic syndrome, disseminated intravascular coagulation, platelet transfusion, pancreatitis, recombinant human thrombomodulin

Introduction

The set of structural abnormalities including vascular damage accompanied by arteriolar and/or capillary thrombosis and characteristic vessel wall thickening with swelling or detachment of the endothelial cell from the basement membrane has been described as thrombotic microangiopathy (TMA).[1,2] Depending on the severity of the disease state, it can manifest with thrombocytopenia, microangiopathic hemolytic anemia, and/or consequent organ dysfunction, predominantly in the kidney and the brain.[1,3] Several conditions, such as the therapeutic use of certain agents, malignant hypertension, and renal transplantation, may lead to TMA,[3–5] but hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) have received focus as 2 major clinical phenotypes of the disease.[1–4] Although the initial pathogenic steps may differ, they eventually merge to a substantial degree, forming the final common processes of injury that result in the consumption of platelets and the intravascular breakdown of red blood cells with almost normal clotting times.[6–9]

In this report, we describe a case of HUS in a thrombocytopenic patient complicated by hemorrhagic colitis due to *Escherichia coli* O157 infection, an increasingly recognized public health problem.[1,2,4,6,8] Several management concerns that emerged in this case are also discussed.

Case Report

A 28-year-old man was admitted to our hospital because of progressive renal dysfunction associated with bloody diarrhea. The patient had consumed half-roasted meat 12 days before

this admission. He had been in excellent health during the next 6 days, but then he began to experience abdominal pain with nonbloody diarrhea and visited a local physician who prescribed fosfomycin, probiotics, and butylscopolammonium bromide. The next day (8 days after the half-roasted meat consumption), he presented at and was admitted to another teaching hospital, as the diarrhea persisted with some stools appearing to consist entirely of blood. A laboratory analysis revealed elevated levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP) at 271 IU/L and 3.6 mg/dL, respectively, as well as obvious leukocytosis of 22590/μL with a serum creatinine (Cr) level of 0.59 mg/dL, hemoglobin (Hb) level of 17.6 g/dL, and platelet count of 28.1×10^4/μL. Diagnostic noncontrast abdominal computed tomography (CT) revealed an inflamed colon (Figure 1A and B). He was therefore presumptively diagnosed with infectious colitis and subjected to empirical ceftriaxone at an intravenous dosage of 1 g every 12 hours combined with volume resuscitation. Despite these managements, the clinical status of the patient steadily worsened, and a second abdominal CT scan performed 3 days later revealed the exaggeration of bowel thickening, distension of the small intestine, and accumulation of ascites (Figure 1C and D) with a serum Cr level of 2.03 mg/dL and LDH level of 2662 IU/L. Other significant changes in laboratory data were a decrease in the Hb level to 11.6 g/dL and in the platelet count to 1.4×10^4/μL. He was therefore transferred and admitted to our hospital for a further workup.

At the time of transfer (hospital day 1), the patient had somnolence with a temperature of 38.3°C, a pulse of 101 beats/
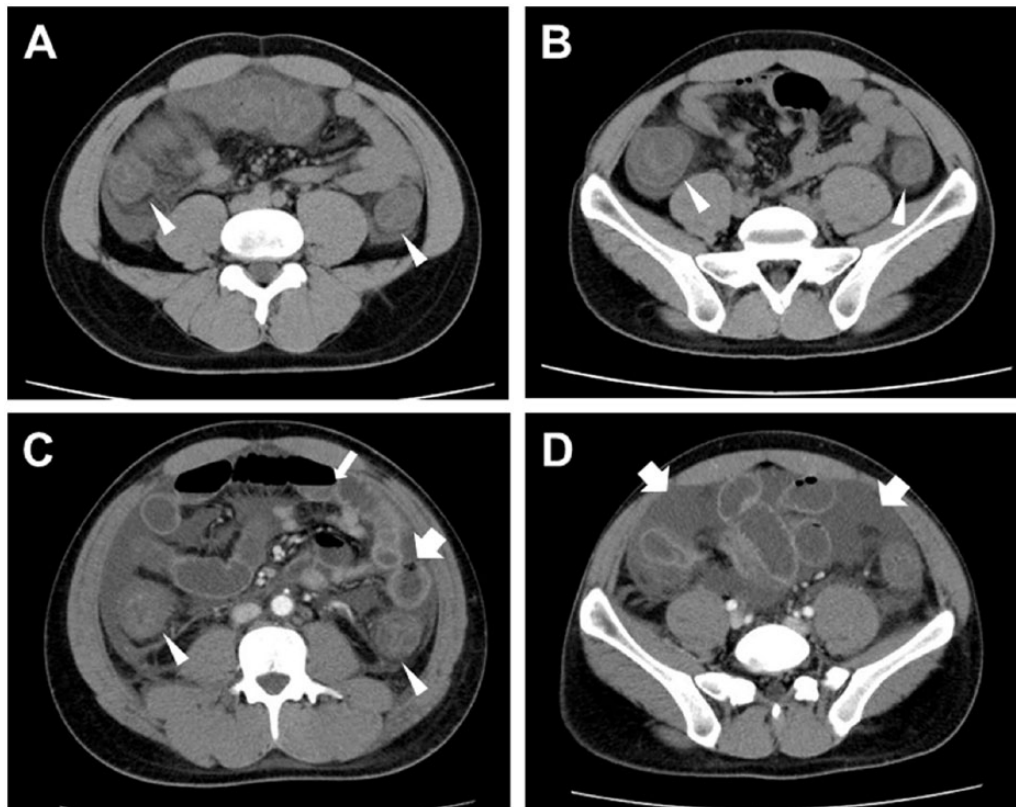
Figure 1. Select axial images of diagnostic abdominal computed tomography. An inflamed colon with circumferential bowel wall thickening (arrowheads) was shown by on initial study (A and B). After 3 days, a second scan (C and D) demonstrated distension of the small intestine accompanied by air-fluid levels (narrow arrow) and the accumulation of ascites (wide arrows) as well as an exaggeration of bowel thickening (arrowhead).

min, and a blood pressure of 108/52 mm Hg. Renal sonography of both kidneys revealed preservation of the size with normal renal cortex echogenicity. The laboratory data on admission to our hospital are shown in Table 1. A decreased level of hapto-globin of <10 mg/dL and schistocytes on peripheral smears were also noted. The results of the patient's bloody fecal culture were unremarkable; however, antibodies to the lipopolysaccha-ride (LPS) of *E coli* O157 were detected by latex agglutination. The patient was then diagnosed with *E coli* O157–mediated hemorrhagic colitis. Based on the laboratory findings, he was also suspected of being simultaneously complicated with dis-seminated intravascular coagulation (DIC).

The day after admission (hospital day 2), a transient session of plasma exchange (PEX), which replaced 3.5 L of plasma with the same amount of fresh-frozen plasma (FFP), was com-menced. Due to the oliguric nature of his renal failure, we decided to apply intermittent hemodialysis (HD) concurrently. Prior to dialysis catheter placement, random-donor platelet concentrates (250 mL, including 400×10^9 platelets) were transfused, resulting in a platelet count of $9.7 \times 10^4/\mu$L. The device was then placed after confirming the patency of the right internal jugular vein by duplex Doppler ultrasound, whereas a hollow fiber polyethylene membrane filter with an average pore size of 0.3 μm and an effective surface area of 0.8 m² (OP-08; Asahi medical Co., Tokyo, Japan) was used as

the plasma separator. Before each session of the PEX, the intravenous administration of 300 mg hydrocortisone sodium succinate was empirically provided as allergic reaction prophy-laxis. The patient was also subjected to supportive management consisting of infusion of antithrombin III (1500 U/day) on 2 consecutive days and intravenous recombinant human throm-bomodulin (rhTM) at 8000 U/day.

He became alert and oriented on the hospital day 3. At this point, his bloody diarrhea disappeared, but laboratory tests revealed increased serum levels of amylase of 310 U/L with pancreatic isoenzyme predominance (99%) and lipase of 801 U/L, indicating concurrent acute pancreatitis; therefore, nafamostat mesilate (NM) was administered not only as a regional anticoagulant for an extracorporeal circuit but also as a therapeutic agent for the disease.[10,11] Thereafter, the patient's urine volume gradually increased along with improvements in his platelet counts as well as serum levels of LDH, so we decided to stop the PEX with HD on hospital day 8 when his platelet count rose to $23.4 \times 10^4/\mu$L. Despite the termination of the systemic treatments with rhTM and NM, his abnormal clotting and fibrinolytic profiles steadily improved, except for a slightly elevated prothrombin time (PT)-international normalized ratio (INR), which was pre-sumptively ascribed to the reduced factor VII activity[12] of 68.4% (reference range: 80.0%-115.0%) found on hospital

Table 1. The laboratory data on admission to our hospital.

White blood cell	19 600/μL	(3900-9800)
Neutrophils	78.6%	(42.0-72.2)
Eosinophils	0.3%	(0.0-5.8)
Basophils	0.2%	(0.0-1.7)
Monocytes	15.6%	(2.5-11.1)
Lymphocytes	5.3%	(19.9-46.1)
Hb	10.0 g/dL	(13.5-17.6)
Platelet count	1.3×10^4/μL	(13.0-36.9)
PT		
Patient's plasma	14.5 s	(10.4-12.2)
Control plasma	11.5 s	
PT-INR	1.29	(0.9-1.2)
Active partial thromboplastin time		
Patient's plasma	36.1 s	(23.1-36.3)
Control plasma	29.9 s	
Antithrombin III	69.9%	(88.0-116.0)
Fibrinogen degradation product	134.9 μg/mL	(0-5)
D-dimer	20.7 μg/mL	(0-1.5)
Blood urea nitrogen	59 mg/dL	(8-20)
Serum Cr	2.15 mg/dL	(0.63-1.03)
Total protein	4.3 g/dL	(6.9-8.4)
Serum albumin	2.0 g/dL	(3.9-5.1)
Sodium	122 mmol/L	(136-148)
Potassium	4.4 mmol/L	(3.6-5.0)
Chloride	89 mmol/L	(96-108)
Calcium	9.6 mg/dL	(8.8-10.1)
Aspartate aminotransferase	74 IU/L	(11-30)
Alanine aminotransferase	15 IU/L	(4-30)
Amylase	106 IU/L	(44-132)
Lipase	96 IU/L	(13-49)
LDH	2422 IU/L	(109-216)
CRP	18.11 mg/dL	(0-0.14)

Abbreviations: CRP, C-reactive protein; Hb, hemoglobin; LDH, lactate dehydrogenase; INR, international normalized ratio.
The reference ranges for each parameter used at our institute are indicated in parentheses.

day 24, and the serum levels of amylase and lipase also decreased gradually but slowly (Figure 2).

He was ultimately discharged on hospital day 31 with an improved sCr level of 0.83 mg/dL, fibrinogen degradation product level of 2.4 μg/mL, and D-dimer level of 0.4 μg/mL. However, an additional 10 weeks were required to confirm the settling of the serum levels of lipase and amylase at around 45 and 96 U/L, respectively. We confirmed the normalized factor VII activity of 80.5%, PT-INR of 1.12, and haptoglobin of 25 mg/dL approximately 8 months after discharge.

Discussion

The main causes of HUS include an infection from enterohemorrhagic *E coli* resulting from intake of contaminated food or water, in which patients present with a gastrointestinal prodrome and genetic or acquired dysregulation of the complement alternative pathway. The clinical presentation of each condition may be similar; however, therapeutic strategies differ depending on the pathogenic basis, and thus a prompt patient investigation to define the underlying etiology is crucial.[1,2,8] In the current case, the stool cultures were negative despite the presence of serum antibodies to *E coli* O157 LPS having been confirmed. Given the difficulty of identifying fecal pathogens among patients with HUS,[13] such a discrepancy may not be surprising, but the lack of an isolated organism prevents any prediction of the potential severity of the disease or determining the serotype.[14] The detection of the antibodies to *E coli* O157 LPS may merely indicate a history of exposure, and the detection of IgM antibodies or demonstration of rising antibody levels may be specific for a recent infection[15]; however, it has been shown that *E coli* O157 fails to induce a long-lasting LPS-specific measurable humoral response in patients with HUS[16]; we therefore believe that the disease of the present patient can be ascribed to *E coli* O157–mediated HUS, although we failed to specify the class profile of the immunoglobulin. Finally, one may argue that some aspects of the clinical scenario of the present patient may be too common to be described in the literature. Furthermore, no brain imaging studies were done to assess the cause of somnolence, which may have been attributable to reversible encephalopathy, presumably resulting from increased vascular permeability.[17] However, the significance of the current report should be evaluated carefully with respect to several management concerns described below.

The mainstay treatment for *E coli* O157–mediated HUS remains supportive and may consist of fluid management, nutrition, and renal replacement treatment, as needed.[1,9] The use of antibiotics, which may favor the acute release of large amounts of preformed toxin, should be avoided, especially during the gastrointestinal phase,[1,8,9] although this was not done in the current patient. It has been stressed that platelet transfusions should be reserved for patients requiring an invasive procedure, such as placement of a dialysis catheter, as there are concerns about worsening the course of the disease through microvascular thrombosis accelerated by the infused platelet
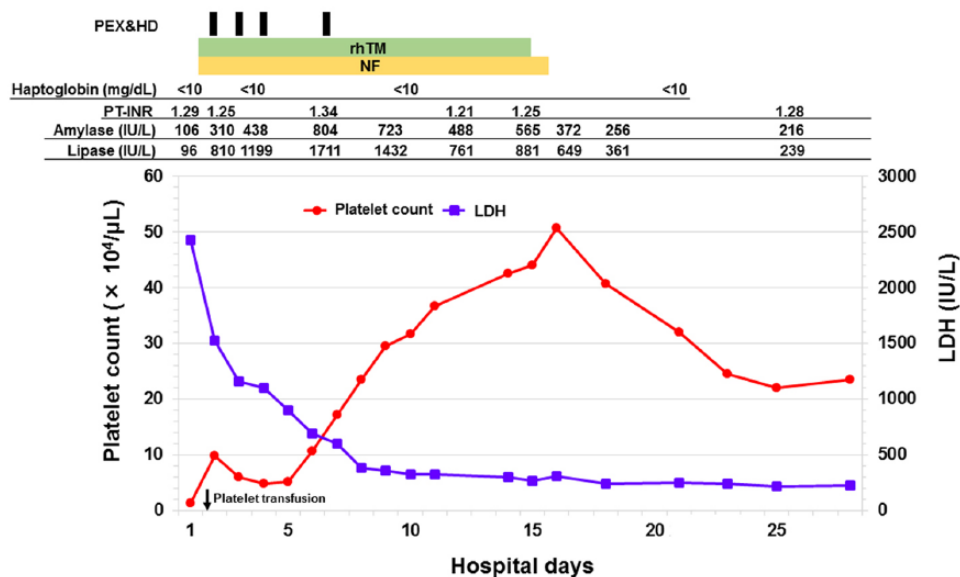
Figure 2. Changes in several clinical parameters during hospitalization. On hospital day 7, the patient no longer manifested thrombocytopenia and showed a recovered platelet count above $15 \times 10^4/\mu L$; however, normalization of the elevated serum LDH levels lagged behind by approximately 3 weeks. Note that PEX combined with intermittent HD (vertical bars on top) was performed on hospital days 2, 3, 4, and 7. HD indicates hemodialysis; LDH, lactate dehydrogenase; PEX, plasma exchange.

concentrates.[18] The severe thrombocytopenia in our patient at transfer obliged us to follow the current recommendations regarding the platelet threshold of $>5 \times 10^4/\mu L$ during the periprocedural period for various invasive interventions, such as lumbar puncture, laparotomy, and the insertion of indwelling lines.[19,20] The validity of employing such a periprocedural management policy in all patients with HUS with severe thrombocytopenia should be assessed comprehensively, as an uneventful central venous catheter placement may not be uncommon among patients with TTP/HUS with platelet counts of $<2 \times 10^4/\mu L$.[21] However, we believe that it is necessary to take a proactive approach before serious hemorrhagic events become apparent. Of note, it has been shown that the platelet transfusions may not necessarily aggravate the course of the disease.[21,22]

Given the prothrombic nature of HUS,[8,23,24] the fact that our patient showed abnormal coagulation profiles including elevated plasma levels of fibrinogen degradation product, D-dimer, and prolonged PT, as well as thrombocytopenia, which met the proposed criteria of DIC,[25] is not surprising, and it might also be unnecessary to list DIC as a separate diagnosis. However, an association between HUS and DIC has been described anecdotally,[26–29] and Vashakidze et al[30] reported their experience, showing that up to 14% of patients with *E coli*–mediated HUS experience DIC during the course of the disease. At present, how to deal with this disease state, which may occur as a result of overactivation of the coagulation pathway through the vigorous binding of factor VII to exposed tissue factor on injured tissue cells,[9] remains unclear. However, this may, at least in part, also explain why the factor VII activity temporarily declined in our patient. The transient inactivation

or accelerated clearance of factor VII might also play a role, as is the case with acquired factor VII deficiency,[31] although we neglected to investigate this possibility in detail. Given the nearly simultaneous application of PEX with FFP, NM, and rhTM, which absolutely modulate the clotting and/or fibrinolytic cascades,[10,11,26,32,33] it is quite difficult to precisely evaluate the therapeutic benefit of each procedure in the present case. Nevertheless, the patient's acceptable outcome prompts us to conclude that our therapeutic regimen was effective for the disease and its complications, despite controversy regarding the indication of PEX in patients with HUS.[9,18,21] The merits of a new treatment modality, such as rhTM, which may work favorably in some subsets of patients with HUS as well as patients with DIC,[23,24,26] should be rigorously examined in systemic randomized trials. In contrast, the efficacy of corticosteroids for preventing allergic reactions in patients who receive PEX therapy with FFP as the replacement fluid remains unclear,[34] although marginal effects with these agents on hematological and/or renal parameters have been shown in patients with HUS.[35] Ultimately, whether or not our patient benefitted from the intravenous administration of hydrocortisone sodium succinate is unclear.

Pancreatitis is another type of organ damage involved in HUS.[36,37] Whereas the pathophysiology predisposing this complication remains unclear, the primary enterotoxin-mediated microangiopathic process may be involved.[37] As a matter of course, serum levels of amylase and lipase should be interpreted carefully in patients with a decreased renal function, as these can be eliminated at least partially by the kidney.[37] Despite repeated ultrasound surveys, we failed to confirm any suggestive findings of pancreatitis, such as

enlargement, a sonolucent pattern, and/or hypoechogenicity,[36,38] in the present patient; however, persistent elevations in the serum amylase and lipase levels even after the resolution of the deteriorated renal function encouraged us to ascribe them to the pancreatitis rather than the diminished renal clearance.[36] A previous single-center study of the gastrointestinal manifestations of pediatric HUS found elevated serum pancreatic enzymes in more than half of patients during the course of their illness, persisting for 10 ± 10 days after the recognition of the disease.[36] Our patient required a longer duration before the normalization of the serum levels of amylase and lipase could be confirmed, implying some discrepancy between pediatric and adult patients in the time course of recovery from pancreatitis complicating HUS. Although the acute pancreatitis seen in HUS may be mild and responsive to conservative management, long-term monitoring for late-onset pancreatic sequelae may be needed in patients with this problem, as some may occasionally progress to permanent glucose intolerance.[36,39]

We hope that the present case will serve as an illustrative example of potentially serious complications of HUS mediated by *E coli* O157 infection. Systemic studies on this topic are insufficient, and the lack of strong recommendations regarding how to manage HUS with various complications implies that numerous therapeutic decisions are potentially empirical. We strongly recommend the prospective accumulation of more experiences similar to our own, thereby allowing us to establish optimum management approaches as well as to clarify the nature of this disease.

Author Contributions

TMu and TA drafted the manuscript. TY, HY, MO, AM, SN, KO, TS, and TMa contributed to the acquisition of the clinical data. TK, OS, SM, and DN provided a detailed review of the contents and structure of the manuscript, resulting in significant changes to the original document. All of the authors have read and approved the final manuscript.

Disclosures and Ethics

As a requirement for publication, the authors have provided the publisher with signed confirmation of their compliance with legal and ethical obligations including, but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) the protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this manuscript is unique and not under consideration for publication or published in any other journals and that they have permission from the rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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