Case Report

J Ped. Nephrology 2014;2(4):154-157
http://journals.sbmu.ac.ir/jpn

Atypical Hemolytic Uremic Syndrome with Severe Extrarenal Manifestations: a Case Report

How to Cite This Article: KOŞAN C, KÜÇÜK N. Atypical Hemolytic Uremic Syndrome with Severe Extrarenal Manifestations: a Case Report. J Ped. Nephrology 2014; 2(4):154-157.

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Atypical hemolytic uremic syndrome (aHUS) is a rare and life-threatening disease that may lead to end-stage renal failure (ESRF) or death, and may be accompanied by a variety of extrarenal manifestations. We presented a child with aHUS accompanied by severe extrarenal manifestations. A 12-year-old girl was visited in the emergency departments with acute renal failure, symptoms of fluid overload, vomiting, and somnolence. Laboratory tests revealed microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure with severe electrolyte imbalance. Diagnosis of HUS was made and emergency hemodialysis was performed to decrease the circulating volume, restore the electrolyte disturbance, and support the treatment of HUS, but conventional medical therapies were ineffective. The patient experienced frequent seizures and multiple cardiac arrests and became comatose. Thereafter, although she was diagnosed with aHUS, plasma infusions and plasmapheresis were performed. Upper gastrointestinal endoscopy and colonoscopy revealed erosive pangastritis, widespread gastric hemorrhagic ulcers, bulbitis, and hemorrhagic colitis. Since there was no improvement, the patient was transferred to a central university hospital where eculizumab was started. She responded to eculizumab. In conclusion, as aHUS can progress rapidly and is frequently fatal if untreated, it is important to be aware of unusual presentations and diagnose the condition promptly, particularly if supportive treatment is of little or no help.

Keywords: Hemolytic-Uremic Syndrome; Hemorrhagic Colitis; Plasmapheresis; Monoclonal Humanized Antibody.

Received: Jun-2014
Revised: Agu-2014
Accepted: Oct-2014

Running Title: Extrarenal involvement in pediatric aHUS.

Introduction

Atypical hemolytic uremic syndrome (aHUS) is defined by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment, usually in the absence of diarrhea. It is a heterogeneous disorder with an insidious onset, a tendency to relapse, and a worse prognosis [1]. Over 50% of aHUS cases are believed to be caused by a genetic defect of alternative complement regulation and the disease is familial in approximately 20% of the cases, with an autosomal recessive or dominant mode of transmission [1-4]. The clinical picture of aHUS is due to various reasons such as defective cobalamine metabolism, infections (Streptococcus pneumonia, HIV, H1N1 virus), HELLP syndrome, drugs (calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, anti-platelet agents, and oral contraceptives), malignancy and systemic lupus erythematosus [5]. Although aHUS predominantly affects the renal microvasculature, extrarenal aHUS manifestations are observed in up to 20% of the patients including the involvement of the central nervous

system (CNS), cardiovascular system, respiratory system, skin, skeletal muscle, and gastrointestinal tract [1,6,7,8,9]. The extrarenal complications may not only be observed during the acute phase of the disease but can also manifest to some degrees years after [1,6,7,8,9,10]. The rates of mortality and morbidity of this group are high, and clinical experience is scanty because of the rarity of these disorders [11]. In the present article, we report the case of a 12-year-old aHUS patient who developed noteworthy extrarenal manifestations including multiple cardiac and respiratory arrests, CNS symptoms such as seizures, consciousness, coma and severe diffuse gastrointestinal ulcers (esophagitis, pangastritis, bulbitis, hemorrhagic colitis) during disease progression.

Case Report

A 12-year-old girl was referred to our institution with complaints of generalized body swelling, oliguria, nausea, vomiting, somnolence, and abdominal pain. Daily urine output was decreased for some days. Her medical history was unremarkable. In her family history, she had three siblings who were all healthy, and her parents had a non-consanguineous marriage.

On physical examination, she had pale skin and conjunctiva, generalized edema, tachypnea (36 breaths/min) and tachycardia (128 beats/min). Her blood pressure was 140/100 mmHg. Her breath sounds were decreased bilaterally at the base of lungs, and there were mild crepitating rales at the middle and lower zones of the lungs. The liver was palpable 4-5 cm below the costal margin. She was admitted to the pediatric nephrology department for further investigations and treatment with a preliminary diagnosis of acute renal failure and pulmonary edema. Laboratory analyses revealed a decreased hemoglobin level (7.2 g/dL), red blood cells (RBCs) (2.3 x 10^6/µL), and thrombocyte count (63 x 10^9/L), and an increased reticulocyte count (20%). Peripheral blood smear revealed schistocytes, burr cells, tear drop cells, anisocytosis, and poikilocytosis. Other test results were determined as BUN: 129 mg/dL, creatinine: 9.2 mg/dL, K: 6.2 mEq/L, Ca: 8.1 mg/dL, P: 8.4 mg/dL, AST: 81 U/L, ALT: 53 U/L, LDH:1773 U/L, haptoglobin: 0.24 g/L (normal range: 0.3-2 g/L), C3: 0.36 g/L (normal range for age: 0.8-1.7 g/L), CRP: 29.4 mg/L (normal range: 0-5 mg/L), and direct Coombs test was negative. ANA, anti-ds DNA, anti-sM, p-ANCA and c-ANCA were all negative. Anticardiolipin IgM and IgG were in the normal range. Von Willebrand factor activity was within normal limits (80.7%; normal range: 50-150%).

Considering the clinical findings and existing laboratory results, she was diagnosed with aHUS, and hemodialysis started for emergency treatment of fluid overload, congestive cardiac failure and biochemical disturbances. Fresh frozen plasma infusions were administered 2-3 times a week, but her vital signs deteriorated as time passed and she developed generalized tonic-clonic seizures and became comatose. Following the transfer to the pediatric intensive care unit on the 30th day of her admission, she suffered from respiratory arrest. She was intubated for 22 days, supported by mechanical ventilation in synchronized intermittent mandatory ventilation (SIMV) and suffered from three cardiac arrests. Cranial tomography revealed no intracranial bleeding or edema. Abdominal and renal Doppler ultrasound examinations, electrocardiogram, echocardiogram, and ophthalmic consultation revealed no pathological findings. After 22 days of intubation, as her general status was stabilized, she was extubated and transferred to the pediatric nephrology ward. Clinical manifestations continued for 40 days, so the patients underwent hemodialysis, plasma infusion and plasmapheresis (50 mL/kg/day for 5 times every other day). Some recovery was noted with plasmapheresis continuing. Maximum C3 and haptoglobin levels were 0.3 g/L and 0.24 g/L, respectively. The reticulocyte percentage remained around 5-6%. During the follow-up, several episodes of bloody, foul smelling diarrhea with mucus were observed. Stool samples were sent for examination repeatedly but no infectious agent was detected. Diarrhea declined during the follow-up, but did not resolve completely. Interestingly, both the platelet count and hemoglobin decreased during the diarrhea episodes. At that time, she was experiencing severe generalized abdominal pain, loss of appetite, severe nausea, and fatigue, and her stools generally contained blood and mucus. Upper gastrointestinal endoscopy revealed loose cardia, erosive pangastritis, gastric hemorrhagic ulcers, and bulbitis. Colonoscopy reported severe hemorrhagic colitis (Figure 1). Blood samples from the patient and her parents were collected for genetic examinations. A mild increase of ADAMTS 13 (1.76 µg/mL; normal range: 0.50-1.60 µg/mL) was reported, and no mutation was detected in factor H gene. The results of other genetic tests were not available when the report was being prepared.

The patient was referred to the department of pediatric nephrology at central university where end-stage kidney failure and active thrombotic microangiopathy were diagnosed by renal biopsy. Eculizumab was initiated after meningococcal vaccination and prophylactic antibiotics were prescribed based on the body weight. The diarrhea episodes, abdominal pain, and general status improved after the treatment with eculizumab (Table1). The patient was then referred to our clinic. Her creatinine level was 2.6 mg/dl and urine output was 100-200 mL/day at admission. She required dialysis, but we stopped hemodialysis and switched to continuous ambulatory peritoneal dialysis due to a vessel problem. She was under observation at our clinic when this report was prepared. She did not require dialysis for five months and her creatinine levels were between 1.5-2.5 mg/dL with 750-1000 mL/day urine output. The patient is still under observation and receives eculizumab with no need for dialysis.

⇧

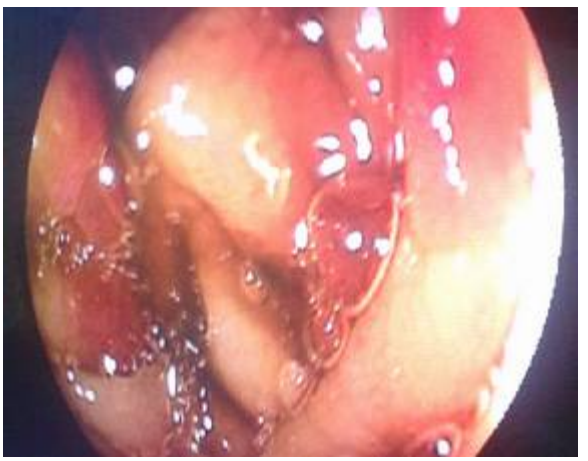

Figure 1. Extensive ulcerative lesions in the patient's colon.

Discussion

Although hemorrhagic colitis has been reported frequently in cases of D+ HUS, it is rarely reported in aHUS. We believe our patient was not a case of D+ HUS due to the fact that diarrhea occurred following HUS, no infectious agent was observed, and diarrhea episodes subsided spontaneously. Furthermore, persistently low levels of C3 and normal ADAMTS 13 strongly suggested that it was a case of aHUS with an as yet unidentified complement disregulation. Hemorrhagic colitis may present as a symptom of aHUS as TMA affects vascular structures systemically, with commonly affected organs including the kidneys, brain, heart, lungs, and the gastrointestinal tract [12,13]. Hemorrhagic colitis was therefore secondary to aHUS and not related to infection. Considering that a diagnosis of aHUS mainly depends on exclusion, detailed and meticulous work-up is required starting from anamnesis. The guideline for the investigation and initial therapy of diarrhea-negative HUS, which was prepared by the European Pediatric Study Group for HUS and published in 2009, currently offers an approach based on opinion to streamline the recognition of such cases in the first month of clinical presentation [14]. More recently, some review articles have summarized current findings [1,5,15,16]. In the present case, absence of familial HUS indicated that it might be a sporadic case of aHUS with life-threatening and rapid deterioration. Hence, life support measures such as hemodialysis and plasmapheresis were intensely employed. As the evidence increases in the literature, we will be able to better define this rare disease in more detail, and optimize individualized treatment according to disease subgroups. In this context, we believe that this case contributed significantly to the available data on extrarenal presentations of aHUS. It also provided an opportunity to test the therapeutic applications of the European Pediatric Study Group for HUS [16].

In conclusion, aHUS may be accompanied by severe hemorrhagic colitis as an extrarenal manifestation. Colonic lesions as a consequence of aHUS should be considered in cases with severe gastrointestinal signs. As aHUS is a rapidly destructive disease with a possible fatal outcome, clinicians should not be reluctant to consider specific therapies like eculizumab if supportive treatments are of little or no help.

Acknowledgments

Medical editing assistance, funded by Alexion Pharma International, was provided by Bioscript Medical.

Conflict of Interest

None declared

Financial Support

None declared

References

1. Loirat C, FrŠmeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis 2011;6:60.
2. Kavanagh D, Goodship T. Genetics and complement in atypical HUS. Pediatr Nephrol 2010;25:2431–2442.
3. Waters AM, Licht C. aHUS caused by complement dysregulation: new therapies on the horizon. Pediatr Nephrol 2011;26:41–57.
4. Westra D, Wetzels JF, Volokhina EB, et al. A new era in the diagnosis and treatment of atypical haemolytic uraemic syndrome. Neth J Med 2012;70:121–129.
5. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. Nefrologia 2013;33:27–45.
6. Riedl M, Fakhouri F, Le QM, et al. Spectrum of complement-mediated thrombotic microangiopathies: pathogenetic insights identifying novel treatment approaches. Semin Thromb Hemost 2014-40:444–64.
7. Meri S. Complement activation in diseases presenting with thrombotic microangiopathy. Eur J Intern Med 2013-24:496–502.
8. Mele C, Remuzzi G, Noris M. Hemolytic uremic syndrome. Semin Immunopathol 2014-36:399–420.
9. Noris M, Remuzzi G. Cardiovascular complications in atypical haemolytic uraemic syndrome. Nat Rev Nephrol 2014-10:174–80.
10. Hofer J, Rosales A, Fischer C et al. Extra-renal manifestations of complement-mediated thrombotic microangiopathies. Front. Pediatr. 2014-2:97.
11. Fitzpatrick MM, Walters MD, Trompeter RS, et al. Atypical (non-diarrhea-associated) hemolytic-uremic syndrome in childhood. J Pediatr 1993-122:532–537.
12. Liptakova A, Siegfried L, Rosocha J, et al. A family outbreak of haemolytic uraemic syndrome and haemorrhagic colitis caused by verocytotoxigenic Escherichia coli O157 from unpasteurized cow's milk in Slovakia. Clin Microbiol Infect 2004;10:576-578.
13. Ullrich S, Bremer P, Neumann-Grutzeck C, et al. Symptoms and clinical course of EHEC O104 infection in hospitalized patients: a prospective single center study. PLoS One 2013;8:e55278.
14. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med 2013;368:2169-2181.
15. Vilalta R, Lara E, Madrid A, et al. Long-term eculizumab improves clinical outcomes in atypical hemolytic uremic syndrome. Pediatr Nephrol 2012;27:2323–2326.
16. Ariceta G, Besbas N, Johnson S, et al.; European Paediatric Study Group for HUS. Guideline for the investigation and initial therapy of diarrhea negative hemolytic uremic syndrome. Pediatr Nephrol 2009;24:687-696.

Table.1 The laboratory results of the case throughout the course of the disease and the treatment type⇧

Days	BUN mg/dl	Creat mg/dl	Hb g/dL	PLT x10³/µL	Haptoglobin (0,3-2 g/L)	LDH (1-248 U/L)	C3 (g/L) (0,9-1,8)	Retic %	Treatment
1	126	9,2	7,2	63	0,24	1773	0,36	20	HD
3	78,5	7,8	8,7	92	0,24	1161	0,49	12	HD+Pİ
14	14,1	2,2	7,5	79	0,24	858	0,79	5	HD+Pİ
28	44,3	5	10,2	182	0,24	603	0,67	9	HD+Pİ
40	25,8	3,3	7,5	229	0,24	614	0,98	8	1.PF + HD
50	20,1	2,2	11,2	168	0,24	371	0,68	4	5.PF + HD
91*	57	6,6	8,1	63	0,24	623	0,32	7	HD+Pİ
98.	60,7	4,3	9,0	247	0,26	329	0,38	4	HD+Pİ
107**	32,2	4,7	8,4	98	0,26	537	0,32	5	HD+Pİ
116	41,5	5,9	8,1	128	0,26	572	0,33	4	HD+Pİ
180	71,4	2,6	13,7	306	1,2	250	0,9	1	*** Eculizumab+HD

HD: Hemodialysis **Pİ:** Plasma infusion **PF:** Plasmapheresis * ,** . The labaratory tests during diarrhea episodes
*** . The labaratory tests after 1 month eculizumab treatment