

A Case of Atypical Hemolytic Uremic Syndrome

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A 9-year-old boy presented with fever not responding to antibiotic therapy and elevated blood urea and serum creatinine levels. The patient developed microangiopathic hemolytic anemia and thrombocytopenia during the hospital stay. Kidney biopsy confirmed the diagnosis of atypical hemolytic uremic syndrome (HUS). The patient had sufficient urine output, normal blood pressure, and no evidence of peripheral edema during the whole course of his disease. Serum levels of anti-Epstein-Barr virus immunoglobulin M was elevated, indicating the possible role of Epstein-Barr virus infection in inducing atypical HUS in this patient. The patient underwent hemodialysis with dramatic response. He was discharged with normal kidney function after a few days. Kidney function and platelet count were normal 12 months after the initial presentation. This case report shows that atypical hemolytic uremic syndrome could have unusual presentations such as the absence of oliguria, hypertension, and edema, with rapid recovery and good prognosis.

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INTRODUCTION

Hemolytic uremic syndrome (HUS) is one of the main causes of acute kidney injury in children. It is defined by the simultaneous presence of acute kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia. Hemolytic uremic syndrome is traditionally classified into typical (with diarrhea) and atypical (no diarrhea), according to its etiology. Typical HUS is the most common type that results from Shiga toxin-producing *Escherichia coli* infection or less commonly *Shigella dysenteriae* type 1 infection.¹ All HUS cases due to other etiologies are classified as atypical HUS, which includes 5% to 10% of all cases of HUS in children.¹ Although atypical HUS can occur at any age, it primarily affects children aging less than 2 years.^{1,2} Atypical HUS usually presents abruptly with pallor, anorexia, vomiting, edema, hypertension, and oliguria. It has poor prognosis with a tendency to relapse within a few months after remission.³ In this case report, we present a child with atypical HUS that had a very unusual clinical presentation and unexpectedly good outcome.

CASE REPORT

A 9-year-old boy was admitted to a local hospital due to high-grade fever and chills. Ceftriaxone and vancomycin were started for the patient with the impression of meningitis. The patient's blood urea nitrogen and serum creatinine levels were normal at the time of admission (Table). Due to unremitting high-grade fever, vancomycin was added to ceftriaxone on the 4th day of admission. After 1 week of antibiotic therapy, the patient was transferred to our center from the local hospital due to the unremitting high-grade fever, appearance of macular skin rash, and rise in blood urea nitrogen and serum creatinine levels. On admission, the patient was febrile with generalized macular skin rash and intermittent episodes of irritability and disorientation. Skin manifestations disappeared soon after discontinuation of the antibiotics; however, fever continued for a few more days.

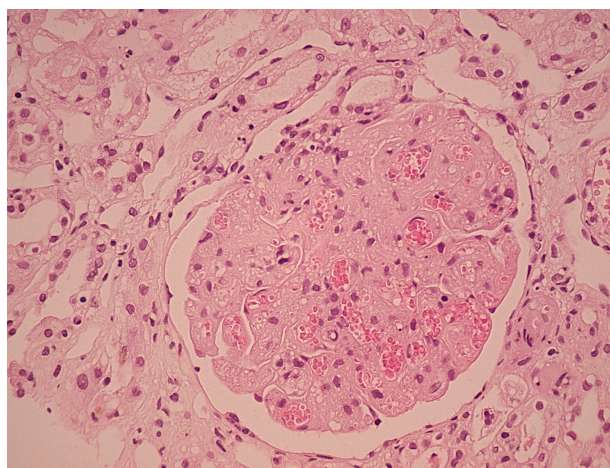
He had no history of diarrhea or respiratory symptoms. His family history was unremarkable. All the laboratory workup for the serum levels of components of complement system, antinuclear

Serial laboratory findings in our patient

Time From Admission	Blood Urea Nitrogen, mg/dL	Serum Creatinine, mg/dL	Hemoglobin, g/dL	Platelet Count, $\times 10^3/L$	Proteinuria	Hematuria
Day 1	13	0.6	10.8	340	0	0
Day 7	34	1.9	11.3	187	1+	0
Day 10	57	2.6	11.0	119	0	3+
Day 13	35	2.0	9.6	79	0	2+
Day 16	10	0.8	7.6	357	0	1+
After 2 months	10	0.8	12.0	650	0	0
After 8 months	12	0.7	12.5	560	0	0
After 12 months	16	0.8	12.7	450	0	0

antibody, antineutrophil cytoplasmic antibody, prothrombin time, and activated partial thromboplastin time were normal, while erythrocyte sedimentation rate and lactate dehydrogenase serum levels were increased. All of the bacterial cultures were negative. Serologic tests for brucellosis and typhoid fever were also negative. Moreover, viral studies by enzyme-linked immunosorbent assay method for all types of viral hepatitis and human immunodeficiency virus were negative. The serum levels of anti-Epstein-Barr virus (EBV) immunoglobulin M (IgM) were elevated, while anticytomegalovirus IgM levels were normal.

After admission, blood urea nitrogen and serum creatinine levels continued to rise gradually. Due to the acute kidney injury and with the impression of tubulointerstitial nephritis secondary to antibiotic therapy, kidney biopsy was performed while the patient had normal platelet count. After a few days, he developed microangiopathic hemolytic anemia, which was evidenced by fragmented erythrocytes on peripheral blood smear, and thrombocytopenia. The pathologic findings of the kidney biopsy were in favor of HUS (Figure). Due to absence of diarrhea and no documented evidence of any bacterial infection, the patient was diagnosed with atypical HUS. Thereafter, hemodialysis and then plasmapheresis were started for the patient. However, due to rapid clinical and paraclinical recovery, including normalization of blood urea nitrogen and serum creatinine levels, only 3 sessions of plasmapheresis were done for him. The patient was discharged without medications with low serum hemoglobin levels as the only abnormal laboratory finding at the time of discharge. Hemoglobin gradually increased to normal levels during the follow-up. The patient was doing well 12 months after the initial presentation with normal blood urea



Fibrin deposition and polymorphonuclear infiltration of renal tissue in favor of hemolytic uremic syndrome (hematoxylin-eosin, $\times 250$).

nitrogen and serum creatinine levels, hemoglobin levels, and platelet count (Table).

DISCUSSION

Although our patient fulfilled the diagnostic criteria for HUS, he had atypical clinical presentations including older age at the initial presentation; absence of oliguria, hypertension, and peripheral edema; rapid recovery; and no recurrence during the 12 months of follow-up. Majority of cases of HUS are due to Shiga toxin-producing *Escherichia coli* or other microorganisms that produce verotoxin in a course of acute enteritis.¹ Etiology of atypical HUS could be genetic, acquired, or idiopathic.⁴ In HUS, tissue damage results from thrombotic microangiopathy, which primarily affects renal blood vessels, leading to vascular wall thickening, thrombosis, and obstruction of vessel lumens.¹ Presence of fragmented erythrocytes in circulation, decreased serum levels of haptoglobin, and increased serum levels of lactate dehydrogenase are all in favor of the intravascular

microangiopathic nature of hemolysis.³

The onset of atypical HUS is usually abrupt. It commonly presents with edema, oliguria, hypertension, and central nervous system symptoms. However, in 20% of patients, atypical HUS could present gradually with mild symptoms.³ In 70% of patients with atypical HUS, the first episode of the disease presents before the age of 2 years; however, atypical HUS can occur at any age, even in the neonatal period.⁵ Hypertension is frequent and is often expected to be severe.³ Central nervous system involvement as the most common extrarenal manifestation of atypical HUS may appear as irritability, drowsiness, seizure, cortical blindness, hemiparesis, or coma.⁶ Urinalysis may reveal hematuria and proteinuria in atypical HUS.³ The initial presentation in our patient was fever and irritability a few days before kidney failure appeared. He also did not develop edema and hypertension probably due to the absence of oliguria. Furthermore, hematuria and proteinuria were mild and transient in our patient.

To date, the association of atypical HUS with different viral infections including rubella, chickenpox, influenza, human immunodeficiency virus, coxsackievirus, echovirus, and EBV has been reported.^{7,8} The elevated serum levels of anti-EBV IgM antibody in our patient indicated that EBV infection might be the cause of atypical HUS.

Management of atypical HUS is mainly supportive. Plasmapheresis has been used with variable success; however, it is still recommended as the mainstay of therapy.¹ Eculizumab and rituximab have been successfully used for control of kidney disease and severe central nervous system manifestations.^{9,10} Relapse of atypical HUS, even after complete recovery, is very frequent. In a recent report from India, atypical HUS in older children had a relapse rate of 80.5% in 70 days.¹¹ Our patient had no relapse during the first 12 months of follow-up. Final outcome of atypical HUS is usually poor, as 25 % die during the acute phase and 50% need long-term renal replacement therapy.¹² In a recent report on 29 children with atypical HUS, only 24.1% had normal kidney function during long-term follow-up.¹³

In conclusion, our case report shows that atypical HUS may have atypical presentations such as absence of oliguria, hypertension, and edema, with rapid recovery and good prognosis.

CONFLICT OF INTEREST

None declared.

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