

An adult case of atypical hemolytic uremic syndrome presented with posterior reversible encephalopathy syndrome: Successful response to late-onset eculizumab treatment

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Abstract

Atypical hemolytic uremic syndrome is a rare and progressive disease caused by uncontrolled alternative complement activation. Dysregulation of the complement activation results in thrombotic microangiopathy and multiorgan damage. A 29-year-old woman who was admitted with complaints of vomiting and headache was detected to have acute renal failure with microangiopathic hemolytic anemia (MAHA). After the diagnosis of atypical hemolytic uremic syndrome (aHUS), she was treated with plasma exchange (PE) and hemodialysis (HD). She has experienced hypertension-related posterior reversible encephalopathy syndrome (PRES) at the second plasma exchange. She was initiated on eculizumab therapy because of no response to PE on the 34th days. Her renal functions progressively improved with eculizumab treatment. Dependence on dialysis was over by the 4th month. Dialysis free-serum Creatinine level was 2.2 mg/dL [glomerular filtration rate (e-GFR): 30 mL/min/1.73 m²] after 24 months.

Neurological involvement (PRES, *etc.*) is the most common extrarenal complication and a major cause of mortality and morbidity from aHUS. More importantly, we showed that renal recovery may be obtained following late-onset eculizumab treatment in patient with aHUS after a long dependence on hemodialysis.

Introduction

Atypical hemolytic uremic syndrome (aHUS) is a rare disorder with an annual incidence of one to two cases per million and progressive disease caused by uncontrolled of the alternative complement activation.^{1,2} Complement regulatory proteins may be damaged in their action by loss-of-function mutations [complement factor H (CFH), complement factor I (CFI), CD46, and thrombomodulin (THBD)] or acquired antibodies (specifically to complement factor H). These genetic mutations reported for 60% to 70% of atypical HUS.^{3,4} Extra-renal manifestations occur in 20% and most commonly involve derangements in the central nervous (altered conscious, seizures or focal neurologic deficits in 8% of adults) and gastrointestinal (prodromic diarrhea in up to 28%) systems.^{5,6} Atypical HUS has a poor prognosis with progression to end-stage renal disease in half the patients.⁷ In patients with thrombotic microangiopathy, plasma exchange should be initiated immediately. The clinical and biochemical response to plasma exchange, typically assessed after 5-7 daily treatments, if accompanied by continued MAHA or absence of renal recovery, treatment with a complement inhibitor may be indicated.⁸ Eculizumab has proven effective against atypical HUS.⁹ This case describes a woman who renal functions and hematological parameters progressively improved with eculizumab treatment with an atypical clinical manifestation of aHUS.

Case Report

A 29-year-old woman was admitted to the hospital in December 2015 with complaints of headache and vomiting for six months, without diarrhea. Her past medical history revealed anemia, normal renal function test and normal MRI performed six months before (she had severe headache the six months ago). On admission, she was anuric, her blood pressure was 150/90 mmHg and there was peripheral edema on physical examination. The laboratory tests at baseline revealed; plasma creatinine: 14 mg/dL (normal range: 0.66-1.09 mg/dL), e-GFR: 6 mL/min/1.73 m² (normal range: >90 mL/min/1.73 m²), urea:188 mg/dL (normal range: 17-43 mg/dL), plasma albumin: 3.2 g/dL (normal range: 3.5-5.2 g/dL), LDH:618U/L (normal range: 0-247 U/L), proteinuria: 5.4 g/L (renal insufficiency and nephrotic syndrome), hemoglobin: 7.2 g/dL (normal range: 11-16 g/dL), platelet: 140x10³/μL (normal range: 100-400

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Key words: Atypical hemolytic uremic syndrome; eculizumab; posterior reversible encephalopathy syndrome, hemodialysis.

Conflict of interest: the authors declare no potential conflict of interests.

Funding: Article processing charge of this manuscript has been granted by the Alexion Pharmaceuticals, Inc.

Received for publication: 26 December 2017.
Accepted for publication: 26 June 2018.

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Hematology Reports 2018; 10:7553
doi:10.4081/hr.2018.7553

10³/μL), with schistocytes on the peripheral blood film (showing existence of microangiopathic hemolytic anemia). Levels of complements C3 and C4 were within normal range. ADAMTS 13 (Von Willebrand factor cleaving protease) was determined as 98% (normal range: 5-10%) effectively excluding thrombotic thrombocytopenic purpura (TTP). An autoimmune screen consisting of anti-nuclear antibody, anti-phospholipid antibody and lupus anticoagulant was negative. C5 and Factor I antigen were normal. Genetic analysis of complement protein genes was mutated at on the complement factor H (CFH -p.Glu936Asp, p.Arg1192Ile) antigen and CFHR5 genes (p.Arg356His) with associated aHUS. However, the importance of heterozygous mutation in C3 (p.Arg834Trp) detected in our patient it is yet to be determined. We have not demonstrated any pathological significance of C3 with aHUS.

She was started on hemodialysis, pulse steroid therapy and plasmapheresis. Renal biopsy was performed due to her deteriorated renal function after hemodialysis. The biopsy revealed that one glomerulus between eight glomeruli was totally sclerotic. There was fibrinoid material on the afferent arteriole of glomerulus and fragmented erythrocytes on one segment of the capillary specimen. There was also minor inflammation at the interstitium (Figure 1).

Our patient had headache, vomiting and high blood pressure. Then later, she develo-

ped generalized tonic-clonic seizures with uncontrolled hypertension after the two cycles of plasma exchange. Her seizures could not be controlled with antiepileptic treatment (diazepam and sodium valproate), and she was connected to mechanical ventilation after status epilepticus. She was then scheduled for chronic hemodialysis programme and twice a day plasmapheresis. The blood pressure was kept under control by antihypertensive therapy. Brain MRI imaging performed after the seizure revealed bilateral symmetrical hyperintensities of the cerebral hemispheres on the fronto-parietal occipital lobes at the T2 secans. This was called posterior reversible encephalopathy syndrome (Figure 2).

On the 34th post-admission day, we started her on eculizumab treatment (weekly intravenous infusion of 900 mg for 4 weeks, followed by a maintenance dose of 1200 mg every 14 days) with prior vaccination against *N. meningococcus* and penicillin prophylaxis. Her renal functions and hematological parameters progressively improved with eculizumab treatment. LDH and creatinine levels decreased within 16 days. Hematological parameters (platelet counts and hemoglobin counts) were normalized within 3 weeks (Figure 3).

Brain MRI findings were normalized after 3 months (Figure 4) and renal function improved by the 4th month. She is still on chronic eculizumab therapy for 24 months. Her blood pressure was kept under controlled with two antihypertensive agents. Hematologic parameters were normal, Dialysis free-serum creatinine level was 2.2 mg/dL (e-GFR=30 mL/min/1.73 m²) at the last follow-up.

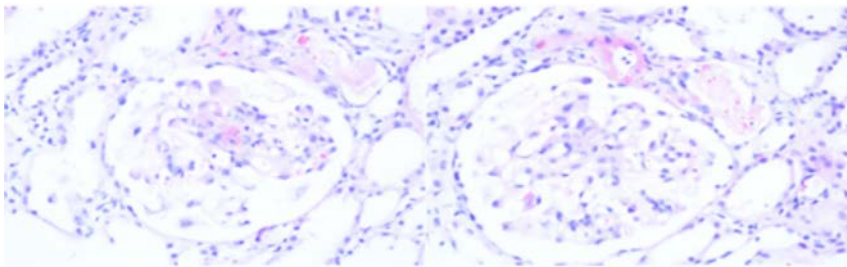


Figure 1. Renal biopsy; histological examination of biopsy revealed fibrinoid material on the afferent arteriole of the glomerulus and fragmented erythrocytes on one segment of the capillary specimen and minor inflammation in the interstitium.



Figure 2. Brain MRI after seizure revealed bilateral symmetrical hyperintensities in the cerebral hemispheres on the fronto-parietal occipital lobes at the T2 secans called posterior reversible encephalopathy syndrome

Discussion and Conclusions

Atypical Hemolytic Uremic Syndrome is a rare and progressive disease caused by uncontrolled of the alternative complement activation. Although thrombotic microangiopathies predominantly affects the renal microvascular, extra-renal manifestations are observed in 20% of patients including involvement of the central nerve system, cardiovascular system, lungs, skin, skeletal muscle, and gastrointestinal tract. Central nervous system manifestations are observed in 20%-50% of cases. These complications are responsible for increased morbidity and mortality.^{1,10}

Central nervous system involvements (irritability, convulsion, hemiparesis and coma) are the most commonly observed extrarenal complications where findings are rarely shown with brain MRI. Two condi-

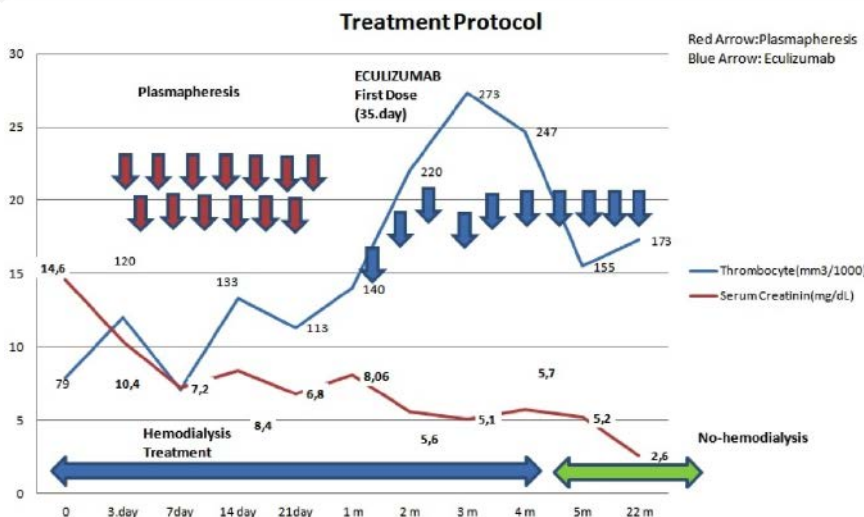


Figure 3. Platelet counts were normalized and serum creatinine level decreased after eculizumab treatment.

ons may be defined radiologically. These are microangiopathic lesion which lesions are bilaterally, symmetric in the thalamus and deep white matter and posterior reversible encephalopathy syndrome (PRES). The neurological clinical features are similar in both conditions. PRES related clinical features are headache, convulsions and coma. They seem usually reversible. In the literature; 120 cases of PRES were identified. The mean age at presentation was 48 years in this study. Primary etiologies of PRES include hypertension, cytotoxic medications, sepsis, thrombotic thrombocytopenic purpura, preeclampsia, eclampsia and multiorgan dysfunction.¹¹ Brain MRI lesions are associated with a posterior white matter hyperintensity and sometimes posterior cortex hyperintensity.¹² These findings were thought to be probably secondary to high blood pressure. PRES related lesions are predominant in parieto-occipital regions. The other lesions described were bilateral thalamus, brainstem and deep white matter involvement.¹³ In our case, lesions were bilaterally symmetrical on the fronto-parietal occipital lobes.

Mutations in complement proteins [CFH, CFI, membrane-cofactor protein (MCP), Complement factor B (CFB), C3 or THMD] as well as antibodies against CFH (CFH-Ab) can be found in around 60-70% of patients with aHUS.^{14,15} Koehl *et al.* reported a first case with cerebral lesions of

atypical HUS. They found a hybrid CFH/CFHL1 gene at the genetic analysis. This mutation causes a susceptibility for aHUS.¹⁶ We found a mutation on the complement factor H antigen and CFHR5 genes associated with aHUS, and also found a heterozygous mutation in C3. However, we

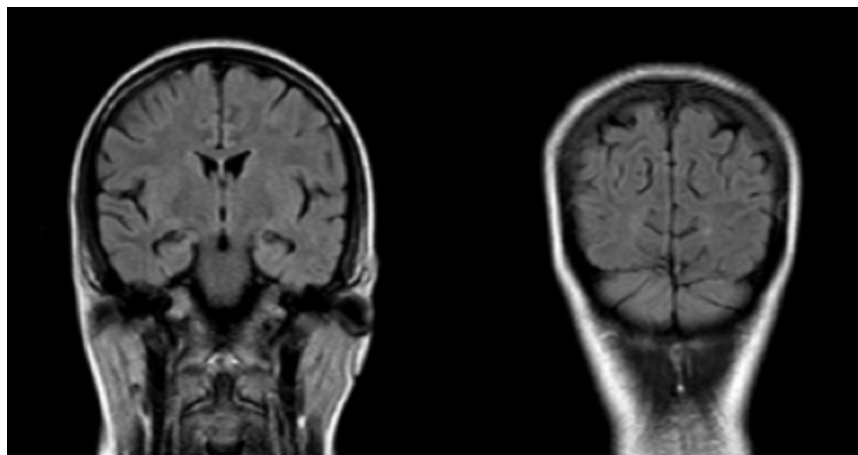


Figure 4. Brain MRI findings were normalized by 3th month after eculizumab treatment.

Table 1. Cases of atypical hemolytic uremic syndrome presented with posterior reversible encephalopathy syndrome and renal failure.

Author	Age	Clinical specifics	Treatment	Renal biopsy result	Genetic analysis of complement protein genes	Hemodialysis/ Renal Tx	Eculizumab response time	Neurological involvement
Duran <i>et al.</i> 2012 ¹¹	28 years	Renal failure, LDH elevation Hemolysis	PE (every-other-day for 1 month, no response)	Showed thrombotic microangiopathy	CFH (c.3514G>T; Glu1172Stop)	HD (4 years) Renal Tx	Started 4 th months, after renal Tx, 2 th months (hematologic, and renal parameters)	No, but severe dilated cardiomyopathy
Koehl <i>et al.</i> 2010 ⁵	4 years	Renal failure, Hypertension	PE (every-other-day for 10 weeks, yes response)	No renal Biopsy	Hybrid CFH/CFHL1	HD (10 weeks) No Renal Tx	No Eculizumab treatment	PRES (4 th weeks of HD and PE)
Gullerog <i>et al.</i> 2013 ⁶	11 years failure	Renal	PE (every-other-day for 1 month, no response)	No renal Biopsy	CFH A307A (rs1061147) CFH H402Y (rs1061170) CFI (E26K and P83T)	HD No Renal Tx	2 th weeks (hematologic, and renal parameters)	PRES (4 th weeks of HD and PE)
Gullerog <i>et al.</i> 2013 ⁶	6 years	Renal failure	PE (every-other-day for 6 days, no response)	No renal Biopsy	MCP L262P	HD No Renal Tx	3 th days (hematologic, neurologic and renal parameters)	PRES (6 th days of HD and PE)
Hu H <i>et al.</i> 2014 ⁷	19 months	Renal failure	HD First line, eculizumab	No renal Biopsy	Unknown	HD No Renal Tx	12 th hours (hematologic, neurologic and renal parameters)	Yes, dilated cardiomyopathy
Povey <i>et al.</i> 2014 ¹⁰	21 years	Renal failure, LDH elevation Hemolysis	PE (every-other-day for 68 days, no response)	No renal Biopsy	C3 (c3466G>A)	HD (82 days) No Renal Tx	14 th days (hematologic and renal parameters)	PRES (8 th weeks of HD and PE)
Our case	29 years	Renal failure, LDH elevation Hemolysis	PE (every-other-day for 34 days, no response)	Showed thrombotic microangiopathy	CFH (p.Glu936Asp, p.Arg1192Ile) CFHR5 (p.Arg356His) C3 (p.Arg834Trp)	HD (34 days) No Renal Tx	16 th days (hematologic and renal parameters)	PRES (2 th days of HD and PE)

LDH, lactate dehydrogenase; PE, plasma exchange; HD, hemodialysis; CFH, complement H factor gene; PRES, posterior reversible encephalopathy syndrome; MCP, membran cofactor protein.

do not yet know the significance of C3 mutation in aHUS etiopathogenesis. Our patient has cerebral lesions on the brain MRI. These findings were normalized by the 3th month after eculizumab treatment.

Gulleroglu *et al.* reported two patients similar with neurological involvement in aHUS and improvement after eculizumab treatment. They achieved complete control of neurological symptoms, renal symptoms and hematological parameters after treatment with eculizumab in these patients.¹⁷ In our case; renal functions, hematological parameters and neurological symptoms progressively improved with eculizumab treatment. Her blood pressure was kept under control with two antihypertensive agents.

Hu *et al.* showed successful treatment with eculizumab in aHUS which presented severe cardiac and neurological involvement. This case received eculizumab within 12 hr of admission, recovered in her neurological state, renal and cardiac function.¹⁸

All cases in the literature presented in children. Our patient was 29 years old. However, presentation tends to be more confusing in adults with aHUS. Diagnosis in the patients may be delayed. Additional biological tests cannot confirm the diagnosis sometimes as 30% of aHUS patients have no complement mutation.¹⁹ However, in our patient, we found mutation on complement factor H (CFH-p.Glu936Asp, p.Arg1192Ile) antigen and CFHR5 genes (p.Arg356His) associated with aHUS and also heterozygous mutation in C3 (p.Arg834Trp). However, we do not yet know the pathological significance of aHUS with the C3 (p.Arg834Trp). In the literature Povey *et al.* reported heterozygous mutation in C3 (c3466G>A) in a patient with aHUS. Their patient presented with renal involvement and received PE and supportive care with HD as first line management, eculizumab therapy was given to the patient on the 3rd month of HD and TMA resolution was provided.²⁰ In another literature study, Duran *et al.* reported a case with TMA recurrence following adult renal transplantation. Their patient also responded to eculizumab.²¹ We started eculizumab treatment on the 34th post-admission day and her renal functions and hematological parameters progressively improved with eculizumab treatment.

As a result, aHUS is a rare and life-threatening disease, and the diagnosis may be delayed despite diagnostic tests. Initial treatment with a course of therapeutic plas-

ma exchange is reasonable while awaiting ADAMTS-13 activity level results in a patient. However, the effectiveness of plasma based therapeutics is associated with genetic back-ground. The cases of continuing hematologic, renal or other clinical manifestations indicates eculizumab. Even when eculizumab treatment is initiated late, it should be taken into consideration that this treatment can cause a dramatic response in these patients.

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