

## Letters to the Editor

# Eculizumab for the treatment of an atypical hemolytic uremic syndrome with mutations in complement factor I and C3<sup>☆</sup>

## Eculizumab para el tratamiento de un síndrome urémico hemolítico atípico con mutaciones en los factores I y C3 del sistema del complemento

Atypical hemolytic-uremic syndrome (aHUS) is a rare, life-threatening complement-mediated thrombotic microangiopathy.<sup>1</sup> Approximately half of cases have mutations in complement proteins but only 12% have 2 or more mutations.<sup>2</sup> Eculizumab is nowadays considered first-line therapy for aHUS.<sup>3</sup>

A 33-year-old female with unremarkable past medical history presented with a 3-day history of decreased urine output. Physical examination showed hypertension (160/90 mmHg) and lower limbs edema. Investigations revealed an acute thrombotic microangiopathy (ATM), hematuria and nephrotic proteinuria (Table 1). Daily plasmapheresis (PMP) was started immediately.

Investigations for secondary causes of ATM revealed a low ADAMTS 13 activity, decreased complement C4, C3, C1q and C2 levels and positive serum cryoglobulins (Table 1). Considering the hypothesis of an autoimmune disorder, we started 3 daily pulses of 1000 mg methylprednisolone followed by oral prednisolone.

PMP was stopped on the eighteenth day of admission (D18) due to normal platelet count during 3 consecutive days (Fig. 1). On the D19 a renal biopsy was made. It showed a "thrombotic microangiopathy with acute tubular necrosis" and "deposition of IgM, C3 and C1q in the capillary wall". Due to increased hemolytic activity, PMP was resumed on the D21. On the D27, rituximab was started to enhance immunosuppression. PMP was stopped on the D35 based on the absence of schistocytosis, hemoglobin stability and lactate dehydrogenase (LDH) normalization.

On the D50, LDH was high but hemoglobin and platelet count were stable. A state of compensated hemolysis was assumed and the patient was discharged home.

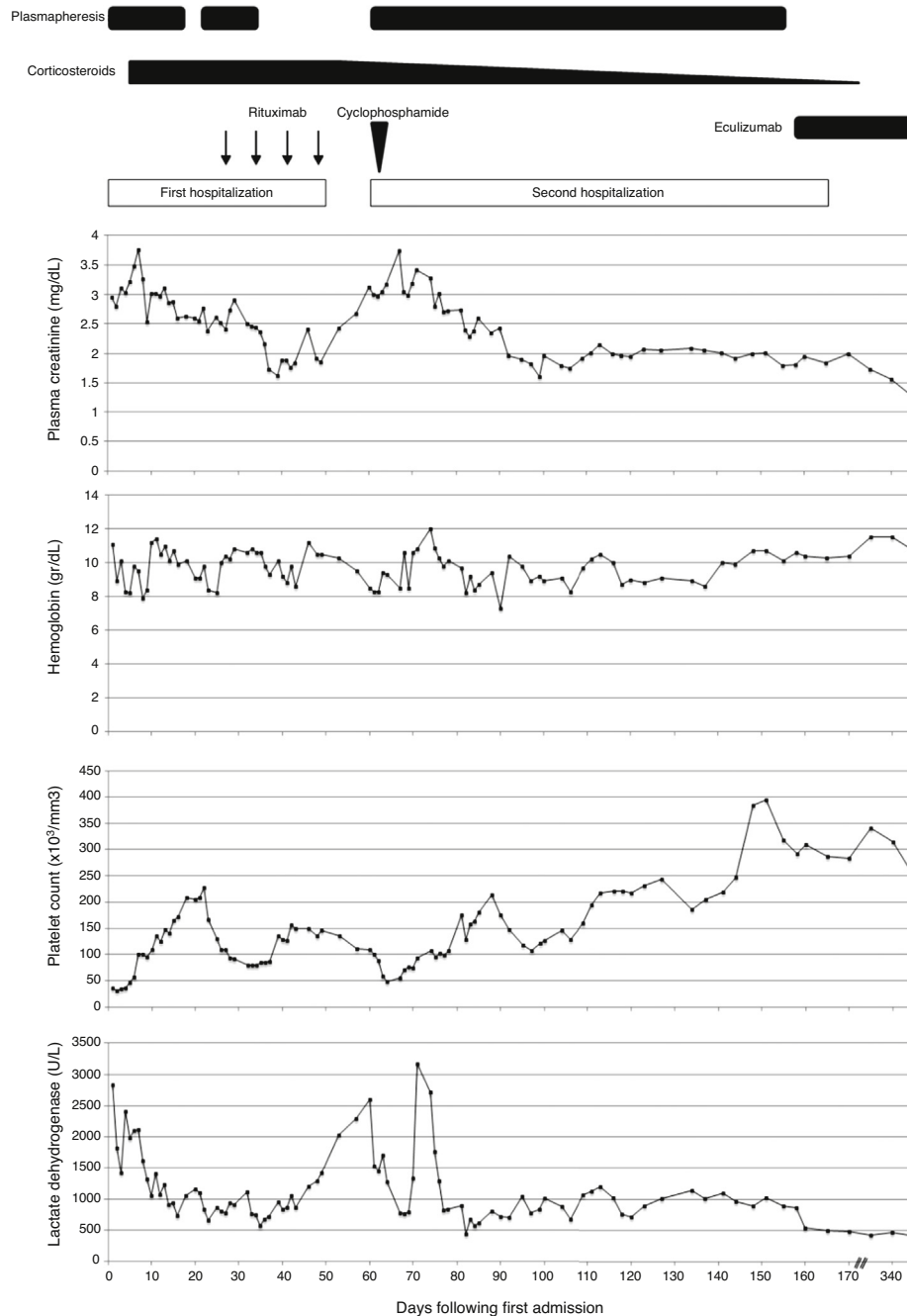
Ten days later she was readmitted due to increased hemolytic activity (Fig. 1). PMP was resumed and 1000 mg cyclophosphamide was given. At that time ADAMTS13 and complement C4 levels were normal but complement C3 levels remained low.

A genetic screening for mutations in complement regulatory proteins was made. Two mutations were found in factor I (C. 452 A>G, pASN 151 Ser) and C3 (C193 A>C, pLys 65 Gin) proteins. The process of eculizumab acquisition was lengthy, wherefore this therapy was started only on the 98th day after readmission. At that moment we were performing one PMP session/week, LDH remained high (859 U/L) and moderate renal dysfunction (creatinine 2.08 mg/dL and urea 60 mg/dL) and nephrotic proteinuria persisted (5.2 g/24 h). Eculizumab was administered at a dose of 900 mg per week for 4 weeks followed by subsequent doses of 1200 mg every 2 weeks since the 5th week. Complete hematologic remission was attained 2 days after eculizumab initiation. The patient was discharged home on the 105th day after readmission. Four weeks later, proteinuria was only 0.6 g/24 h.

Currently, 10 months after first infusion, the patient remains under biweekly administration of eculizumab. Hematologic remission persists and there is a significant recover of renal function (urea 43 mg/dL, creatinine 1.27 mg/dL).

Complement factor I (CFI) and C3 mutations account for 10% and 4% of the overall aHUS-associated mutations, respectively.<sup>3</sup> C3 mutations are among the ones with the poorest prognosis: 75% risk of death or end stage renal failure (ESRF) at 3–5 years follow up and 50% risk of recurrence.<sup>3</sup> CFI mutations have a 50–60% risk of death and ESRF at 3–5 years follow up and 10–30% risk of recurrence.<sup>3</sup>

<sup>☆</sup> Please cite this article as: Ferreira E, Oliveira N, Marques M, Francisco L, Santos A, Carreira A, et al. Eculizumab for the treatment of an atypical hemolytic uremic syndrome with mutations in complement factor I and C3. *Nefrologia*. 2016;36:72-75.



**Fig. 1 – Clinical course: laboratory data and treatment.** Corticosteroid therapy was started with intravenous administration of methylprednisolone (1000 mg/day for 3 days) followed by oral prednisolone and an initial dosage of 60 mg/day. This dosage was maintained until the 53rd day after admission, with posterior tapering. Rituximab (arrows) was administered at a dose of 600 mg (375 mg/m<sup>2</sup>) on the 27th, 34th, 41st and 48th days after admission. Cyclophosphamide (arrowhead) was administered in a single dose of 1000 mg on the 61st day after admission (2nd day after readmission). Eculizumab was administered at a dose of 900 mg for a week for 4 weeks, started on the 158th day after admission, followed by a dosage of 1200 mg 1 week later and then a maintenance dose of 1200 mg every 2 weeks. This dosage is still being continued. We performed a total of 79 plasma exchange sessions. The last three laboratorial test results were done on the 270th, 340th and 466th days following first admission.

Both mutations present in our patient were previously reported.<sup>4,5</sup> The p.Asn151Ser mutation causes a quantitative deficiency of factor I<sup>4</sup> and the p.Lys65Gin mutation weakens the affinity of C3b to complement factor H.<sup>5</sup>

Despite the growing importance of eculizumab,<sup>6,7</sup> PMP remains the mainstay of treatment while waiting for the immunoglobulin.<sup>3</sup> Nonetheless, its benefit depends on the underlying genetic defect – only 25% and 57% of those with CFI and C3 mutations, respectively, achieve remission.<sup>8</sup> In our

**Table 1 – Laboratorial results on admission and additional studies to establish the cause of the thrombotic microangiopathy.**

On admission		
Variable	Result	Normal range
Hemoglobin (g/dL)	11.1	12–16
White-cell count ( $\times 10^3/\text{mm}^3$ )	7.6	4–10
Platelet count ( $\times 10^3/\text{mm}^3$ )	36	150–400
Peripheral blood smear <sup>a</sup>	10 schistocytes	<2 schistocytes
Haptoglobin (g/L)	<0.08	0.3–2
Direct coombs tests	Negative	Negative
Urea (mg/dL)	114	15–38
Creatinine (mg/dL)	2.9	0.52–1.04
Sodium (mmol/L)	135	137–145
Potassium (mmol/L)	3.6	3.5–5.1
Lactate dehydrogenase (U/L)	2827	313–618
c-Reactive protein (mg/dL)	0.6	<1.0
URINALYSIS		
Protein (mg/dL)	1000	
Leukocytes (/HPF)	3	<5/c
Red blood cells (/HPF)	28	<2/c
Urinary protein to creatinine ratio (mg/mg)	14	<0.15
Additional studies		
Variable	Result	Normal range
C3 (g/L)	0.46	0.9–1.8
C4 (g/L)	0.02	0.1–0.4
CH50 (U/mL)	13	23–46
C1q (mg/L)	39	118–244
C1q Inhibitor (mg/L)	197	180/320
C2 (mg/L)	7.2	14–25
ADAMTS13 activity (%)	7%	40–130
Anti-ADAMTS13 antibody (U/mL)	Negative	<15
Serum cryoglobulins	Positive	
Auto-immune antibodies <sup>b</sup>	Negative/Normal	
Pregnancy test, SPE, Tumoral markers <sup>c</sup> , HIV, HBV, HCV		
Blood, urine and stool cultures	Negative	
Upper endoscopy, colonoscopy, cervical, thoracic and abdominopelvic CT	Irrelevant changes	

<sup>a</sup> Peripheral blood smear was done to evaluate presence of erythrocyte fragmentation and is reported as schistocytes count in a microscopic field at 100 $\times$  magnification.

<sup>b</sup> Antinuclear antibodies, extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies, glomerular basement membrane, rheumatoid factor, cyclic citrullinated peptide, anticardiolipin/anti- $\beta$ 2-glycoprotein, Lupus anticoagulant.

<sup>c</sup> Carcinoembryonic antigen, carbohydrate antigen 19-9,  $\alpha$ -fetoprotein, cancer antigen 125, neuron-specific enolase, NSE. Abbreviations: ADAMTS13; a disintegrin and metalloproteinase with a thrombospondin type 1 motif; member 13. CT; computerized tomography. HBV; hepatitis B virus. HCV; hepatitis C virus. HIV; human immunodeficiency virus. SPE; serum protein electrophoresis.

patient, PMP was critical to prevent further progression of renal failure and the development of other systemic involvement. However, as described by Loirat,<sup>2</sup> it was unable to achieve complete and sustained remission.

In our case, the confounding presence of low ADAMTS13, C4, C2 and C1q levels, the presence of cryoglobulins and the

existence of immune deposits in the glomerular capillary wall led to the misdiagnosis of a thrombotic thrombocytopenic purpura secondary to an autoimmune disease. It explains the preference for glucocorticoids, rituximab and cyclophosphamide in relation to eculizumab.<sup>9</sup>

Eculizumab is nowadays considered first-line therapy for aHUS.<sup>3</sup> It is a humanized monoclonal immunoglobulin IgG that targets C5 and blocks the uncontrolled generation of the cytotoxic membrane attack complex.<sup>10</sup> When we started Eculizumab, our patient was still PMP dependent despite the 79 PMP sessions. Contrariwise, complete hematologic remission was attained two days after first infusion and a remarkable recover of renal function and reduction of proteinuria was evident. These findings reinforce the benefits of eculizumab in aHUS, even in cases of severe renal involvement.

In conclusion, our case highlights the diagnostic challenge of aHUS and emphasizes the notion that isolated PMP is no longer the best therapeutic option in aHUS, in which cases a prompt switch to eculizumab is mandatory.

The authors declare that they have no conflicts of interest related to the contents of this article.

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## Methylmalonic acidemia with emergency hypertension<sup>☆</sup>

### Acidemia metilmalónica con hipertensión de emergencia

Dear Editor,

Methylmalonic acidemia (MMA) is a heterogeneous disorder of propionate metabolism. MMA is caused by deficiency of the mitochondrial enzyme, methylmalonyl-CoA mutase-*apoenzyme* activity (MUT) or defective in adenosylcobalamin (coenzyme) synthesis.<sup>1</sup> The most patients with cblA and half patients with cblB forms of MMA are responsive to vitamin B12.<sup>2,3</sup> Clinical manifestation of MMA may be acute or chronic. The acute form of the disease occurs during infancy and even as early as the second day of life with poor feeding, vomiting, dehydration, weight loss, temperature instability, lethargy, hypotonia, seizure and progressing to coma. Laboratory findings include: metabolic acidosis, ketosis, hypoglycemia, hyperlactatemia, hyperammonemia, pancytopenia.<sup>4</sup>

Definitive diagnosis of isolated MMA is based on analysis of organic acids in plasma and/or urine; however genetic testing diagnosis in some condition is accessible to confirm the diagnosis of isolated MMA. Below, we describe the presentation and management of two cases of MMA with severe hypertension.

The first case was a 46-day-old girl, admitted to the emergency department because of generalized edema and severe hypertension. She was born from consanguineous parents at term with a birth weight 2.600 kg. She had frequent vomiting in 9th day of life. Edema of hands and feet appeared in 39th day of life. On admission, she had SBP 130 mmHg (above 99th), DBP 75 mmHg (above 99th), periorbital and legs pitting edema and respiratory distress. Laboratory findings included: microscopic hematuria, massive proteinuria, hypoalbuminemia, pancytopenia and high anion gap metabolic acidosis.

The patient was managed by nephrologists with diagnosis of congenital nephrotic syndrome. Angiography of abdominal aorta and renal artery were normal. She had brain atrophy and supra and infra tentorial ventriculomegaly in brain

CT scan and left ventricular hypertrophy in echocardiography. Abdominal sonography was normal but both kidneys were seen larger than normal. Bone marrow aspiration (BMA) was performed because of pancytopenia which was normal. Patient's hypertension did not respond to Losartan, Hydralazine, Captopril and Amlodipine. Metabolic consulting and then metabolic tests due to refractory metabolic acidosis was done. The patient with suspected organic aciduria was treated with hydroxycobalamin 1 mg daily, biotin 10 mg daily and L-carnitine 50 mg/kg/day. She had high level of glycine in blood amino acid chromatography but ammonia, lactate, serum B12 and homocystein were normal. Methylmalonic aciduria confirmed with high level of urine methylmalonic acid and increased serum level of propionyl carnitine. We have increased the dose of B12 up to 2 mg IM daily but unfortunately, the patient died.

The second case was a 45-day-old boy admitted from the emergency ward with complaints of anemia, respiratory distress and severe hypertension. He was born from non-consanguineous parents at term with a birth weight 2.800 kg. The first baby of the family had died at the age of 5-months due to propionic aciduria. On examination he had respiratory distress (RR = 67), SBP 134 mmHg (above 99th) and DBP 78 mmHg (above 99th) and mild pitting edema in legs. Laboratory results included: high anion gap metabolic acidosis, pancytopenia, hypoalbuminemia, proteinuria, and microscopic hematuria. Lactate, ammonia, serum B12, serum homocystein and other electrolytes were normal but serum glycine was increased. Renal artery disorder has been excluded by Doppler sonography. Abdominal sonography was normal but both kidneys had upper normal size and increased cortical echogenicity. BMA was performed because of pancytopenia which was normal. According to the familial history and our previous case, after sending samples for urine organic acid, acylcarnitine profile and chromatography of serum amino acid, B12 2 mg IM daily,

<sup>☆</sup> Please cite this article as: Yaghmaei B, Rostami P, Varzaneh FN, Gharib B, Bazargani B, Rezaei N, et al. Methylmalonic acidemia with emergency hypertension. *Nefrologia*. 2016;36:75–76.