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CASE REPORT

Complement-Mediated Hemolytic Uremic Syndrome: Management Challenge behind the Diagnosis - A Case Report

Ana Carlota Vida*, João Carvão, Pedro Vieira, Luís Resende and Gil Silva

Department of Nephrology, Hospital Central do Funchal, Madeira, Portugal

***Corresponding author:** *Ana Carlota Vida, Department of Nephrology, Hospital Central do Funchal, Avenida Luís de Camões 6180, 9000-177 Funchal, Madeira, Portugal*

Abstract

Acute thrombotic microangiopathies (TMA) represent an heterogeneous group of diseases, including complement-mediated hemolytic uremic syndrome (CM-HUS). CM-HUS results from an alternative complement pathway dysregulation as a result of mutations in complement factors or antibodies against these factors. It is important to exclude secondary causes of TMA before establish CM-HUS as a final diagnosis. However, this may be challenging, since complementary evaluation is not always immediately available. Since Eculizumab approval, there was a modification in disease's course, decreasing progression to end-stage-renal disease (ESRD). We present a case of a young woman, who presented with severe TMA manifestations and acute kidney injury. Management included therapeutic plasma exchange (TPE) and then Eculizumab initiation, when CM-HUS was diagnosed. Despite the temporary necessity of hemodialysis, there was total recovery of kidney function. CM-HUS is a rare diagnosis with a high morbimortality and early recognition is fundamental to allow the initiation of targeted treatment.

Keywords

Thrombotic microangiopathy, Complement mediated hemolytic uremic syndrome, Therapeutic plasma exchange, Eculizumab

Abbreviations

CM-HUS: Complement Mediated Hemolytic Uremic Syndrome; CT: Computerized Tomography; ESRD: End Stage Renal Disease; LDH: Lactate Dehydrogenase; STEC-HUS: Shiga Toxin-producing *Escherichia Coli* associated Hemolytic Uremic Syndrome; TMA: Thrombotic Microangiopathy; TPE: Therapeutic Plasma Exchange; TPP: Thrombotic Thrombocytopenic Purpura

Introduction

Acute thrombotic microangiopathy (TMA) is classically characterized by the triad of hemolytic anaemia (Coombs negative), thrombocytopenia and organ damage. Endothelial lesion and dysfunction results in platelet activation and aggregation leading to thrombus formation in small vessels with subsequent occlusion, hypoxia and ischemia of tissues. Despite similar clinical manifestations, the pathophysiology varies according to the aetiology of the disease [1].

In the group of TMA, complement-mediated Hemolytic Uremic Syndrome (CM-HUS) is a rare exclusion diagnosis, accounting for nearly 10% of cases [2]. Physiopathological mechanisms are related with an alternative complement pathway dysregulation. It can occur as a result of complement gene mutations or presence of antibodies against complement factors and various triggers can contribute to it [3]. However, the absence of identifiable mutations in complement proteins does not eliminate the possibility of a CM-HUS [4].

Alongside anaemia, intravascular haemolysis (elevated Lactate Dehydrogenase (LDH), decreased haptoglobin, reticulocytosis and presence of schistocytes) and acute kidney injury, patients may have multiple concomitant presentations. Through the kidney involvement one may present with haematuria, oedema and hypertension [3]. Other extra-renal manifestations include gastrointestinal presentations

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such as nausea, vomit, diarrhea, colitis, abdominal pain or pancreatitis; neurological symptoms such as altered mental status, seizures and focal neurologic deficits; cardiac involvement with myocardial infarction, myocardiopathy and heart failure besides other organ involvement [1,5].

The diagnosis is essentially clinical, though it relies on exclusion of Thrombotic Thrombocytopenic Purpura (TTP), Shiga toxin-producing *Escherichia coli* associated Hemolytic Uremic Syndrome (STEC-HUS), and secondary causes of TMA such as infection, malignancy, pregnancy, autoimmune diseases and drugs [6]. This distinction may be challenging however decisive to establish management and therapy. For that, normal activity of ADAMTS13 and absence of antibodies against this enzyme, allow exclusion of TTP; as negative culturing for Shiga toxin rules out STEC-HUS [7].

Actually, notwithstanding the cause or trigger of CM-HUS, this entity by itself has a high morbimortality, conditioning a poor prognosis. During the acute phase, mortality rate is up to 10 to 15% and about 50% of cases progress to end-stage renal disease (ESRD) [2]. Therefore early recognition is fundamental, since therapy should be promptly initiated.

Case Report

We report a case of a 22-year-old Caucasian woman from Brazil, with medical history of an ischemic stroke at age of 8-years-old and an auricular myxoma, submitted to surgery. She first presented to the Emergency Department (ED) with nausea, vomiting and epigastric pain for four days. Her blood evaluation revealed anaemia (Hb 10.3 g/dl), acute kidney injury (serum Creatinine 1.93 mg/dl and Urea 69 mg/dl), LDH 536 U/L, indirect hyperbilirubinemia (1.72 mg/dl) e high Reactive-C Protein 91.55 mg/L. Despite these results, the patient abandoned the hospital before any medical intervention or follow-up.

She then presented to the ED, five days later, with worsening of the previous symptoms, along with fever, abnormal urine odour and choluria. There was no recent history of diarrhea or drug ingestion. Physical exam revealed normal blood pressure, pallor and signs of dehydration, no cutaneous lesions or neurological signs. Analytical evaluation showed a significant aggravation of anaemia (Hb 7.8 g/dl), thrombocytopenia, acute kidney injury (serum Creatinine 3.96 mg/dl, Urea 96.5 mg/dl); LDH 1392 U/L; high sedimentation rate (> 140 mm) and C Reactive Protein (104.52 mg/L). Urinalysis revealed leukocyturia, erythrocyturia and proteinuria (Table 1). A Computerized Tomography (CT) scan was performed and it revealed bilateral pleural effusion and renal asymmetry, with the right kidney measuring 128 × 78 × 65 mm and an atrophic left kidney (60 × 34 × 30 mm) - with no documented hydronephrosis.

Nephrology collaboration was requested and considering the classical triad of hemolytic anaemia, thrombocytopenia and acute kidney injury, a diagnosis of TMA secondary to pyelonephritis was assumed, in a patient with only one-functioning kidney. Antibiotic therapy was started with Ciprofloxacin as well as vigorous fluid hydration.

Despite this, there was an aggravation of the symptoms in the following 72 hours, with generalized headache, vomiting and new onset hypertension. On physical examination there were no neurological signs and cranial CT scan did not reveal any acute lesions. Analytical evaluation evidenced a worsening of hemolytic anaemia (Hb 6.3 g/dl, Platelets 85000/uL, Schistocytes 6%, LDH 889 U/L, negative Coombs Test), undetectable haptoglobin and progressive deterioration of kidney function (serum Creatinine 4.12 mg/dl), although preserved diuresis. At this moment, while diagnosis work-up on causes of TMA was still on course, support therapy with therapeutic plasma exchange (TPE) was initiated on a daily regime, using reposition with Human Albumin 5% and fresh frozen plasma.

Additional study allowed the exclusion of secondary causes of TMA, such as infectious (negative cultures of blood, urine and stool; Epstein-Bar Virus, Cytomegalovirus, B19 Parvovirus, hepatitis B and C and Immunodeficiency Virus were all negative); autoimmune (including antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, lupus anticoagulant, anticardiolipin antibodies and beta2-microglobuline were all negative; normal complement (C3 and C4) and normal Immunoglobulins); or pregnancy and cyanocobalamin deficiency. Thorough imagiological study did not raise suspicion of malignancy.

After three sessions of TPE, there was an improvement of symptoms and haemolysis parameters, despite worsening of kidney function (serum Creatinine 4.87 mg/dl). Six days after admission, results from ADAMTS13 were obtained, revealing normal activity, with no antibodies, allowing exclusion of TTP. A diagnosis of CM-HUS was assumed and Eculizumab, anti-C5 monoclonal antibody, was initiated at 900 mg. Prophylactic measures as vaccination (anti-meningococcal, anti-pneumococcal and *Haemophilus influenzae b*) and amoxicillin were instituted. Eculizumab initiation prompted the delay of TPE to an alternate day prescription.

At day 8, clinical worsening was reported, with headache, arterial hypertension and aggravation of anaemia (Hb 6.1 g/dl), thrombocytopenia (103,000/µL), rise on schistocytes count (5.2%) and kidney worsening (serum Creatinine 5.18 mg/dl), so another session of TPE was performed followed by a supplemental dose of Eculizumab (600 mg).

At day 10, due to presenting oliguria, hypervolemia as for bilateral pleural effusion and hypoxemia with

Table 1: Analytical evaluation on admission.

	On admission	Normal range
Hemoglobin (g/dL)	7.8	11.9-14.9
White-cell count (10^3/µl)	8400	4200-10,800
Neutrophils (10^3/µl)	6.0 (77.5%)	1.9-7.2
Platelets (10^3/µl)	79	144-440
Reticulocytosis (%)	2.8%	0.6-2.7
Peripheral Blood Smear	Without schistocytes	-
Haptoglobin (mg/dl)	< 7.69	30-200
Direct coombs test	Negative	-
PT (seg)	12	9.4-12.5
INR	1.02	0.9-1.2
PTT (seg)	30	25-37
Urea (mg/dl)	96.5	8-50
Creatinine (mg/dl)	3.96	0.7-1.2
Sodium (mmol/L)	135	136-145
Potassium (mmol/L)	4.5	3.5-5.1
Sedimentation Rate (mm)	> 140	0-20
C-Reactive Protein (mg/L)	104.52	≥ 6.10
Lactate Dehydrogenase (U/L)	1392	0-246
Bilirubin Direct/Indirect (mg/dl)	1.56/0.27	0-1.1/0-1.2
ALT (U/L)	28.8	14-54
AST (U/L)	51.9	10-35
ALP (U/L)	92.6	30-120
GGT (U/L)	76.0	7-50
Albumin (g/dL)	24.1	35-48
Urinalysis		
Proteins (mg/dl)	400	
Leukocytes (/µL)	91.67	0-36
Red blood cells (/µL)	45.47	0-25
Urinary Protein to Creatinine ratio (g/g)	12.369	0-0.200

PT: Prothrombin Time; INR: International Normalized Ratio; PTT: Partial Thromboplastin Time; ALT: Alanine Transaminase; AST: Aspartate Transaminase; ALP: Alkaline Phosphatase; GGT: Gama-Glutamyl Transferase

limited response to diuretic therapy, the patient was submitted to a single haemodialysis session with isolated ultrafiltration. After this, there was a progressive recuperation of diuresis. Also, a transfusion of one unit of blood was performed.

At day 13, new dose of Eculizumab was administered. By this time, analytical and clinical improvement was evident as for gradual recovery of anaemia (Hb 7.9 g/dl) with descent of haemolysis parameters and serum Creatinine, independent of plasmapheresis or dialysis (Table 2).

The scheme of Eculizumab was maintained: 900 mg at 0, 7, 14, 21 days; at week five, a dose of 1200 mg was administered and a biweekly scheme was kept. After the first month of treatment, analytical results revealed continuous improvement, as for anaemia (Hb 8.4 g/dL), normalization of platelets counts, with no signs of active haemolysis, and serum Creatinine of 2.37 mg/dl. The molecular complement study did not identify any pathogenic variant. However, it revealed a heterozygote deletion at *CFHR3* and homozygote deletion at *CFHR1*, which are considered risk factor for CM-HUS. The functional complement study presented a slight decrease in Factor H. There were no anti-factor H antibodies.

On the follow-up, the patient showed sustained clinical stability and no evidence of disease reactivation, along with kidney function recovery - serum Creatinine of 1.0 mg/dl, six months after this event. After one year, the patient remained with stable kidney function (serum Creatinine 0.82 mg/dl) and proteinuria (Urinary Protein/Creatinine Ratio 0.859 g/g) with no relevant complications. Suspension of this treatment is not foreseeable considering the high risk of disease relapse.

Discussion

This case illustrates the importance of a high index of suspicion concerning CM-HUS hypothesis and the necessity of excluding several other causes before settling it as a final diagnosis. The clinical picture of pyelonephritis lead us to think first of a TMA secondary to infection, but there was no improvement with treatment. There was a clinical and analytical worsening of TMA and TPE was initiated, while investigation was still on course. A kidney biopsy could help us establish the diagnosis, but due to an atrophic left kidney and assuming only one functionating kidney, this possibility was withdrawn. In fact, results from ADAMTS13 activity and antibodies, necessary to diagnose PTT, are not always immediately available. Considering that, the PLASMIC score is a helpful tool to assess the risk of severe ADAMTS13 deficiency in patients with TMA [8]. This distinction is relevant, as in the case of CM-HUS complement blockage should be initiated promptly [9].

Since the approval of Eculizumab in 2011, the prognosis of patients with CM-HUS has evolved and is associated with better outcomes, in terms of renal recovery and platelet count normalization [10]. This humanised monoclonal antibody binds to the C5 complement component, blocking the formation of membrane attack complex responsible for mediating microangiopathic lesions. Therefore, in patients with diagnosis of CM-HUS, Eculizumab is first line therapy and evidence supports its efficacy and safety [9,11]. Nevertheless, in cases where the diagnosis is still unclear or in centres where this drug is unavailable or of difficult attainment, TPE should be initiated, especially in patients with severe manifestations of TMA [5,11].

In our case, despite TPE and later Eculizumab initiation, there was progressive deterioration of kidney function with need of one session of isolated ultrafiltration due to refractory hypervolemia, underlying a congestive cause. Though, kidney response was more evident about one week after Eculizumab was initiated and then sustained, allowing TPE discontinuation.

Concerning complement study, it was relevant for deletions of *CFHR3* and *CFHR1*. It is described in literature that deletions in *CFHR1* e *CFHR3* are associated with the formation of Anti-factor H antibodies [11]. In our case, even though we did not identify any anti-factor H antibodies, these mutations are risk factor for HUS. Noris, et al. observed that polymorphisms and mutations of *CFH* are found in a majority of patients with secondary CM-HUS, thus suggesting a genetic predisposition [2].

Regarding the adequate duration of Eculizumab therapy, it is not yet established and it is controversial [11,12]. Some authors defend undetermined continuation of this treatment, considering the risk of relapse and severity of the disease [5]. However,

Table 2: Analytical evaluation since admission and management approach.

	Day of admission	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 15	Day 20
Hemoglobin (g/dL)	7.8	7.8	7.2	6.3	7.4	7.6	7.0	6.4	6.6	6.1	6.3	6.2	8.3	7.9	7.2	8.0
Platelets (10^3/µl)	79	79	85	85	111	130	131	135	170	203	196	202	207	245	221	287
Schistocytes (%)	0	1.0	4.6	6.0		4.8	6.5	8.2	7.1	7.5	7.8		6.3		3.9	2
LDH (U/L)	1392	1094	980	889	679	720	685	657	471	389	445	439	431	455	392	435
Serum Creatinine (mg/dl)	3.96	3.36	3.72	4.12	4.64	4.87	4.78	5.18	4.73	5.07	5.43	5.39	5.25	4.93	4.56	3.06
Management				TPE	TPE	TPE	ECU	TPE	TPE ECU	HD		1 Unit RBC		ECU		ECU

Note: LDH: Lactate Dehydrogenase; TPE: Therapeutic Plasma Exchange; ECU: Eculizumab; HD: Hemodialysis; RBC: Red Blood Cells

this approach is not exempt of risk, as meningococcal infection, which requires maintenance of antibiotic prophylaxis. Therefore, the decision of suspension must be individualized, considering that according to documented mutation, the risk of relapse is different [9]. In this case, we have a very young patient with a severe presentation, that only has one functioning kidney, and in which a new relapse may precipitate and progress to ESRD. For this reason, we intend to maintain this therapy.

Concluding, CM-HUS is an entity which needs an extensive evaluation to establish the final diagnosis. Its management is challenging as despite supportive therapies, the course is variable and sometimes unpredictable. We want to highlight the impact of TPE in an initial phase but, at the same time, the importance of prompt complement blockage initiation, as this measure changed the course and prognosis of this disease.

Conflict of Interest

The authors declare that there are no conflicts of interest associated with this manuscript.

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