A case of renal recovery in atypical hemolytic uremic syndrome treated with eculizumab

Um caso de recuperação da função renal na síndrome hemolítico-urêmica tratada com eculizumab

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Abstract

Atypical Hemolytic Uremic Syndrome (aHUS) is a rare, life-threatening disease that can occur at any age and be sporadic or familial. aHUS is caused by an uncontrolled activation of the complement system. Plasma Exchange (PE) has been the standard treatment for years with poor results, leading approximately 40% of patients to end-stage renal disease (ESRD) or death during the first clinical manifestation. Eculizumab, an humanized monoclonal antibody directed against complement component C5, has emerged in the last few years as a new therapheutic aproach with promising results. Our goal is to present a case of an adult patient where eculizumab was sucessfully used as upfront therapy avoiding the potential significant morbidity of PE.

Keywords: acute kidney injury; hemolytic-uremic syndrome; thrombotic microangiopathies.

Resumo

A síndrome hemolítico-urêmica atípica (SHUa) é uma doença grave, pouco prevalente, com acometimento em qualquer idade e apresentação esporádica ou familiar. A SHUa é causada por uma ativação descontrolada do sistema complemento. A plasmaférese foi o tratamento padronizado por anos, com resultados desfavoráveis, levando à doença renal crônica terminal ou morte em aproximadamente 40% dos pacientes durante as primeiras manifestações clínicas. O Eculizumab é um anticorpo monoclonal humanizado contra o componente C5 do complemento e nos últimos anos vem sendo utilizado como novo arsenal terapêutico com resultados promissores. O presente caso descreve uma paciente adulta tratada com eculizumab em que se obteve resultados satisfatórios evitando-se potenciais riscos e aumento da morbidade com o procedimento de plasmaférese.

Palavras-chave: lesão renal aguda; microangiopatias trombóticas; síndrome hemolítico-urêmica.

Introduction

The thrombotic microangiopathy (TMA) syndromes are extremely diverse in its presentation, could be acquired or hereditary and may affect children and adults.[1] The pathological process of microangiopathic haemolytic anemia (MAHA), consumptive thrombocytopenia and microvascular thrombosis are the cardinal clinical features present in this condition, leading to organ injury. Patients mostly have acute kidney disease and brain dysfunction; cardiac, gastrointestinal and other organ injury may be present though.[1,2] The histological features are vascular damage that comprise arteriolar and capillary thrombosis, altered vessel walls and endothelium surfaces.[1-3]

There are primary thrombotic microangiopathy disorders classified based on their probable causes such as thrombotic thrombocytopenic purpura (TTP), complemente-mediated TMA, also known as atypical haemolytical uraemic syndrome (aHUS), shiga toxin-mediated hemolytic-uremic syndrome (ST-HUS), drug-mediated TMA, metabolism-mediated TMA, coagulation-mediated TMA.[1] Many patients have microangiopathic hemolytic anemia and thrombocytopenia that are manifestation of an underlying disease (Table 1).[1,2]

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Table 1 Differential diagnosis of MAHA and thrombocytopenia

Systemic Infections: viral (HIV, cytomegalovirus), fungal (Aspergillus), bacterial
Systemic cancer, cancer chemotherapy, ionizing radiation
Pregnancy: HELLP syndrome, severe preeclampsia, eclampsia
Malignant Hypertension
Autoimmune disorders: systemic lupus erythematosus, antiphospholipid syndrome, systemic sclerosis, vasculitis
Hematopoietic stem-cell or organ transplantation

Note: table adapted from George et al.[1], Barbour et al.[2], Tsai et al.[3]

Atypical haemolytical uraemic syndrome is a complement-mediated TMA caused by and uncontrolled terminal complement activation of the alternative pathway.[1-4] Mortality and end-stage renal disease (ESRD) approaches 33-40% of acute phase aHUS cases.[4] Despite plasma exchange or plasma infusion, 65% of all patients have at least one of these complications in the first year after the diagnosis: requirement of dialysis, ESRD or death.[3,5]

Anticomplement therapy is an important tool currently available for management of aHUS.[1-9] Eculizumab is the first recombinant humanized monoclonal anti-C5 antibody that prevents the activation of the terminal complement pathway, preserving the proximal pathway.[1-9] It is an effective therapy and it emerges as a first-line treatment for aHUS.[1-9] Here, we report a case of aHUS successfully treated with eculizumab as upfront therapy.

Case report

Female, 35 years-old, presented complaining with dyspnea, nausea and oliguria initiated 6 days before admission. She referred flu-like symptoms 15 days before. Her past medical history was unremarkable. At admission into the Emergency Department the patient's vital signs was a blood pressure of 160/90 mmHg, pulse rate of 120 beats/min, respiratory rate of 26 breaths/min, oxygen saturation in room air of 94%, axillary temperature of 36,5 °C. On physical examination, she presented jaundice in sclera, pale mucous membranes and a mild edema in legs bilaterally. The cardiac and pulmonary auscultation were normal. The laboratory tests on admission are illustrated at Table 2.

Acute renal failure was managed with hemodialysis and clinical support was maintained. Laboratory tests collected to investigate viral hepatitis, human immunodeficiency virus, pregnancy, ANA (antinuclear antibody), direct Coombs, lupus anticoagulante, anticardiolipin antibodies, ANCA (anti neutrophil cytoplasmic antibodies), anti-glomerular basement membrane antibodies, leptospirosis IgG and PCR (polymerase chain reaction) and stool cultures were negative. The quantitative dosage of the complement fractions (C3- Beta 1C e C4-Beta 1E) was at normal range. An abdominal ultrasound evidenced normal morphology of the kidneys, diffuse increased echogenicity of renal parenchyma billaterally and loss of corticomedullary differentiation, signs suggestive of parenchymal nephropathy and the renal artery doppler ultrasound was normal. In view of the clinical and laboratory data, this case suggested the diagnosis of thrombotic microangiopathy. The sequencial investigation included serum ADAMTS13 activity - disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 - and renal biopsy. The result of ADAMTS 13 activity was 55% (reference value > 70%) and the histological findings on renal biopsy was thrombotic microangiopathy), presence of crescents in two of the thirteen glomerulus and absence of chronic tubule-interstitial damage (Figure 1 and 2). The immunofluorescence staining panel revealed granular and diffuse segmental IgM deposits in glomerular capillary loops. IgA, IgG and C3 analysis was negative.

Supported by the diagnosis workup the patient received the diagnosis of aHUS and we choose to use eculizumab as upfront therapy. After meningococcal prophylaxis, we started the patient on eculizumab 1200 mg weekly for 4 weeks and after 900 mg every 15 days. During the first months of treatment there was complete hematological remission and continuous improvement of the renal function (Figure 3). The patient discontinued hemodialysis and the current estimated glomerular filtration rate is 73.2 mL/min per 1.73 m^2. She maintains outpatient treatment with eculizumab 900 mg every 15 days.

Discussion

There is no objective diagnostic criteria for aHUS and this disease could share clinical manifestations with other TMA syndromes.[1,10] The promptly recognition of a suspected case is essential to the

Table 2 Laboratory tests on admission

Laboratory Test	Result	Reference Value
Hemoglobin (g/dL)	3.9	12 - 16,5
Leukocytes (cel/mm^3)	11590	4.500 - 11.000
Platelets (mm^3)	83000	150.000-450.000
Peripheral Blood Smear	Schistocytes +/4+	-
Reticulocytes (%)	11.39%	0.5-2.5%
Lactate Dehydrogenase (U/L)	875	125 -220
Creatinine (mg/dL)	13.7	0.57-1.11
Urea (mg/dL)	167	15-44
Prothrombin Time (RNI)	1.02	0.8-1,2
Activated Partial Thromboplastin Time (ratio)	0.77	0.8-1.2
Albumin (g/dL)	3.4	2.9-5.2
Total Bilirubin (mg/dL)	7.07	0.1-1.2
Indirect Bilirubin (mg/dL)	5.25	< 0.20
Total Calcium (mg/dL)	8.3	8.6-10.3
Inorganic Phosphorus (mg/dL)	4.4	2.3-4.7
Sodium (mEq/L)	132	136- 145
Potassium (mEq/L)	4.5	3.5-5.1
Aspartate Aminotransferase (U/L)	35	5-34
Alanine Aminotransferase (U/L)	31	2-55
Urinalysis	Protein +, Hb+++, Bilirubin+	-

Figure 1. Glomerulus showing mesangiolysis and peripheral loops containing fragmented erythrocytes and luminal microthrombi. There is proliferation of parietal epithelium with incipient crescent formation.

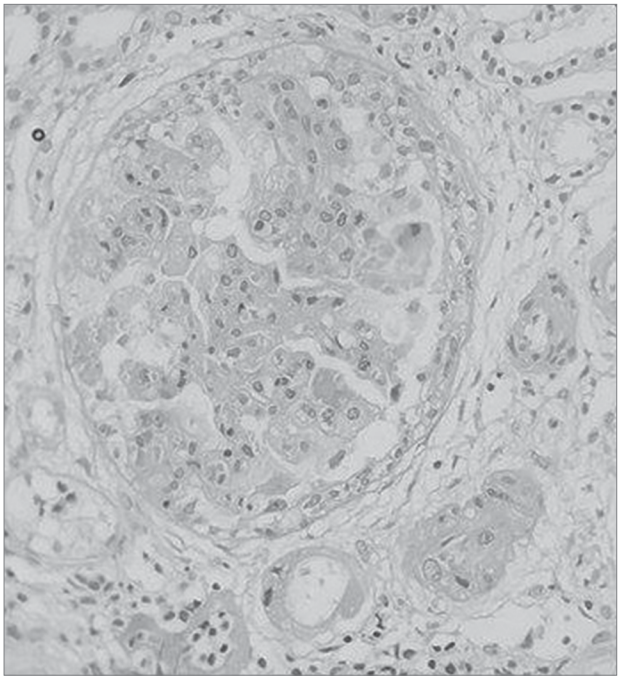
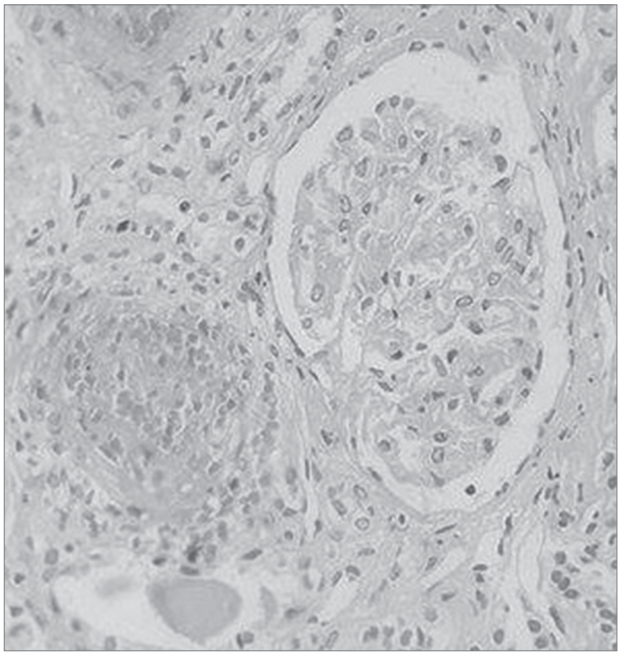
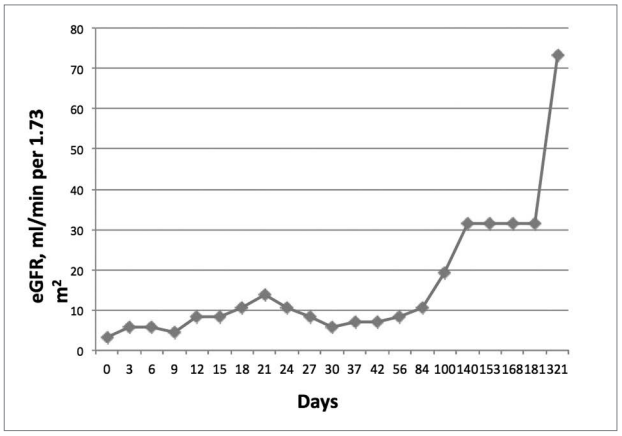


Figure 2. Arteriole showing intense fragmentation of erythrocytes in the lumen and wall and signs of mucinous degeneration of media.



specific management of aHUS and it modifies clinical outcomes for patients.[4,10] Recent studies reported that some laboratory data can accurately predict patient's pretreatment ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity, severely deficient in most cases of acquired TTP, which helps in the differentiation between aHUS and TTP.[10] The findings of platelet count < 30 X 109/L and serum creatinine ≤

Figure 3. Renal function improvement during treatment.



2.25 mg/dL have been associated with severe deficient ADAMTS 13 activity.[10]

It remains useful to obtain pretreatment ADAMTS 13 activity, because it helps clinicians in the correct management of patients in the majority of cases. However, this exam should not be used alone to guide treatment.[10] The current management of aHUS consists in plasma exchange (PE), eculizumab, liver and kidney transplant.[11] Historically, PE has been the standard of care in patients with aHUS, but PE proved beneficial for short term hematologic remissions in aHUS, however end stage renal disease rates still high.[7,12,13] It remains a treatment option which brings to the patient possible serious morbidities such as transfusion related adverse events and usually requires a central venous line that raises the rates of sepsis and thrombosis in patients submitted to the procedure.

Recently, the physiopathological basis of many kidney diseases is linked to complement cascade dysregulation and the complement system is now recognized as an important mediator of transplant injury. Blocking the complement cascade in kidney transplant recipientes could be an option to improve graft and patient survival rate. Some pathogenetic similarities with aHUS indicate anti-C5 therapy as treatment option for C3 glomerulopathies.[14]

Eculizumab is a humanized monoclonal antibody that blocks the proinflammatory and the cytolytic effects of terminal complement activation. It binds to complement C5, block the cleavage of C5 into C5b, hinders the generation of proinflammatory C5a and the potentially lytic C5b-9 (membrane attack) complex.[1-4]

The anticomplement therapy with eculizumab in aHUS proved to achieve hematological remission, promoted stabilization or improvement in renal function with reported cases of discontinuation of dialysis, increased the TMA event-free status for patients and it reduced mortality.[7,11,13] The most frequently reported adverse reactions with this treatment were headache, hypertension, cough, upper respiratory tract infections, urinary tract infections, nausea, vomiting, diarrhea, abdominal pain, anemia and leukopenia.[8,11] Eculizumab therapy augment the risk of meningococal infections and the vaccination against *Neisseria meningitidis* should be done at least two weeks prior the treatment. Patients usually need promptly therapy and a 2-week course of antibiotics may be administered.[8,11] The optimal duration of long-term treatment with eculizumab remais to be definied.[7,8,10] The very high probability of aHUS in this case, even without results of genetic tests, guide us to initiate eculizumab as first-line therapy without previous plasmapheresis.[15] The anticomplement therapy needs to be started as soon as possible to stop TMA progression and to avoid irreversible organ damage, improving patient's prognosis.[4,7,10,15]

In conclusion, eculizumab clearly modified the clinical course of the disease, with improvement of hematological and renal dysfunctions, without severe adverse effects. The anticomplement therapy was a landmark in aHUS management and more studies have to be done with eculizumab as initial treatment for aHUS.

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