Atypical haemolytic uraemic syndrome. Two cases

Síndrome hemolítico-urêmica atípica. Relato de dois casos

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ABSTRACT

Haemolytic uraemic syndrome is a disfunction known as thrombotic microangiopathy. When it is not caused by Shiga toxin, produced by *Escherichia coli*, the disease is called atypical, which is classified in primary and secondary. This paper aims to study two case reports diagnosed as atypical haemolytic uraemic syndrome secondary to calcineurin inhibitors. Both are patients that had undergone kidney transplantation, but lost their graft due to atypical haemolytic uraemic syndrome. Their presentations were pancytopenia for one and anaemia of difficult management for the other, the first one was taking the medication called tacrolimus and the second one was taking cyclosporine. Nephrotoxicity related to the usage of calcineurin inhibitors was already known since it was introduced in the medical practice, however its efficacy in the control of graft rejection may exceed the problems regarding side effects. Nevertheless, it was observed that in long terms, the morbidity related to these side effects are indeed relevant. Therefore, new medicines and therapeutic schemes capable of lowering exposure to calcineurin inhibitors are being studied. There are two options of treatment established to atypical haemolytic uraemic syndrome and both of them were used in the case reports presented in this paper: plasmapheresis or plasma infusion and eculizumab, an antibody that blocks the complement system pro inflammation, pro thrombotic and lytic functions. There is great discussion regarding which one of these treatments are the most suitable for atypical haemolytic uraemic syndrome. However, the choice of the therapy depends of each patient, individually, as was seen in the cases presented in this article.

Keywords: Hemolytic-uremic syndrome; Kidney transplantation; Calcineurin; Tacrolimus; Cyclosporine; Case reports

RESUMO

A síndrome hemolítico-urêmica (SHU) é uma disfunção caracterizada por microangiopatia trombótica (MTA). Quando sua causa não é devido à toxina Shiga, produzida por *Escherichia coli*, ela é dita atípica, que se classifica em primária e secundária. Este artigo visou relatar dois casos clínicos de síndrome hemolítico-urêmica atípica secundária ao uso de inibidores da calcineurina, para os quais foram feitos os seguintes diagnósticos diferenciais: púrpura trombocitopênica trombótica, síndrome hemolítico-urêmica atípica primária, anemia hemolítica autoimune e hemoglobinúria paroxística noturna. Ambos os casos eram pacientes transplantados renais que sofreram perda do enxerto devido à síndrome hemolítico-urêmica atípica; um estava em uso de tacrolimo, enquanto a outra paciente estava em uso de ciclosporina. A nefrotoxicidade relacionada com o uso de inibidores da calcineurina já era conhecida desde sua introdução na prática clínica, entretanto sua eficácia no controle da rejeição do enxerto superava as preocupações em relação às reações adversas. Porém observou-se que, a longo prazo, a morbidade relacionada a essas reações é significativa e, hoje, os estudos buscam novos medicamentos e esquemas terapêuticos capazes de diminuir a exposição aos inibidores da calcineurina. O tratamento estabelecido para síndrome hemolítico-urêmica atípica era de plasmaferese e/ou infusão de plasma, mas, em 2011, foi aprovado o uso de eculizumabe, um anticorpo que bloqueia as funções pró-inflamatórias, pró-trombóticas e líticas do complemento. O uso de eculizumabe para tratamento dessa enfermidade é ainda recente, mas já demonstra benefícios em relação ao tratamento de plasmaferese e infusão de plasma.

Descritores: Síndrome hemolítico-urêmica; Transplante de rim; Calcineurina; Tacrolimo; Ciclosporina; Relatos de casos

INTRODUCTION

Atypical haemolytic uraemic syndrome (aHUS) is a dysfunction characterized by thrombotic microangiopathy (TMA), defined by thrombocytopenia, hemolytic anemia, and renal impairment.[1]

The aHUS clinical cases are those that do not occur due to Shiga toxin, synthesized by *Escherichia coli.* They are classified in primary or secondary aHUS. The first one is consequence of deregulation of complement system that occurs either because of a genetic mutation or because of presence of auto-antibodies against factor H, a regulatory protein that is component of complement system.[1]

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The second group is related to several situations, such as: infectious agents (*Streptococcus pneumoniae* and H1N1 influenza A); chemotherapy and ionizing radiation in cancer treatment; blood marrow or organ transplantation; intake of calcineurin inhibitors; sirolimus or anti- vascular endothelial growth factor (VEGF) agents; pregnancy; hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome; glomerulopathies; malign hypertension; systemic diseases (systemic lupus erythematosus, sclerodermia, antiphospholipid syndrome).[2]

This paper aimed to present and study two aHUS cases secondary to calcineurin inhibitors. Both are kidney transplant patients that lost their grafts due to aHUS.

CASE 1

Male, 58 years old, received a kidney transplant 14 years ago. The patient had been experiencing progressive loss of his graft in the last 6 months, period in which he was undergoing dialysis. Physical examination showed pallor (3+/4+), bruises on superior limbs, bilateral cervical adenopathy, afebrile, acyanotic, no signs of jaundice, nor visceromegaly. He was intaking: azathioprine, tacrolimus, atenolol, amlodipine, furosemide, omeprazole. Exams showed pancytopenia (Table 1).

Ganciclovir was administrated because blood tests showed positive IGM for cytomegalovirus. However, the patient had a progression of pancytopenia, reticulocytosis, enhancement of LDH, schistocytes were found in peripheral blood and decrease of haptoglobin, suggesting TMA (Table 1).

Treatment with frozen fresh plasma infusion began, 15mL/, three times per week, after haemodialysis sessions, throughout 1 month, after which there was normalisation of platelet, high-density lipoprotein (LDH), reticulocytes, haptoglobin, besides that there were no more signs of hemolysis, and they have remained stable since then (Table 1). ADAMTS13 was tested: 67%, which was indicative that the patient did not have thrombotic thrombocytopenic purpura (TTP). Results of direct Coombs and the imunophenotyping for Paroxysmal nocturnal hemoglobinuria (PNH) clone detection were also negative.

CASE 2

Female, 26 years old, received a kidney transplant 10 years ago. She was referred to department due to anemia of difficult management that had been lasting for 8 months (Table 1) despite several attempts of treatment with blood transfusion. The patient had comorbidities: hypertension, Turner syndrome, and positive detection of hepatitis C virus. She was taking cyclosporine, mycophenolate mofetil, atenolol, B vitamins, prednisone, and folic acid. Physical examination was normal apart from skin and mucosa pallor, besides moon face.

The glomerular filtration rate was 30mL/min, the patient presented with reticulocytosis, thrombocytopenia, normocytic anaemia without anisocytosis, and negative direct Coombs. Even though the cyclosporine was suspended after 4 months of follow-up because of interstitial fibrosis tubular atrophy, the patient progressed with proteinuria and loss of kidney draft. Because of the high levels of lactate dehydrogenase (LDH) reticulocytosis, and decreased levels of haptoglobin and hemoglobin the hypothesis of TMA was established.

The imunophenotyping for PNH clone detection did not show presence of PNH clones. ADAMTS13 levels were also tested, but as the results were of 77% the diagnosis of TTP was excluded. The frozen fresh plasma infusion started, 15mL/Kg, 3 times per week, throughout 1 month. Although it resulted in improvement of platelets level and hemolysis (Table 1), the treatment was suspended due to the difficulty in managing the hypertension, hypervolemia and congestive heart failure. It was then started the treatment with eculizumab. After the third dose of the medicine the platelet levels had already been normalised around 100.000/mm^3, there was improvement of reticulocytosis and the LDH and haptoglobin levels were normalized again (Table 1). After 3 months of treatment with eculizumab, the total complement factors reached 159mg/dL, C3 was 93mg/dL and C4 14,7mg/dL.

DISCUSSION

The syndrome aHUS is an outcome of the faulty regulation of the complement system, which can be either inherited, acquired or both and leads to a chronic uncontrolled activation of the complement system, resulting in TMA.[3]

Several factors might precipitate aHUS, such as respiratory tract infections, pregnancy, drugs, and diarrheal disorders caused by other agents rather than *E. coli*. Even though when there is not a previous diagnosis of aHUS, the aforementioned "activation" is possible if the patient is exposed to a trigger, as in a situation of transplantation.[4]

Table 1. Laboratory data from patients 1 e 2

	Patient 1		Patient 2		
	In the beginning of investigation	After frozen fresh plasma infusion	In the beginning of investigation	After frozen fresh plasma infusion	After infusion of eculizumab
Haemoglobin (g/dL)	5.91	10.3	8.7	8.7	9.2
Platelets/mm^3	84,000	210,000	112,000	104,000	116,000
Leucocytes/mm^3	2,200	5,300	3,800	3,800	5,400
LDH (U/L)	1,174	220	703	576	402
Haptoglobin (mg/dL)	<5.8	143	5.8	100	115

LDH: high-density lipoprotein.

In the clinical cases presented earlier, both patients developed the disease because of the intake of calcineurin inhibitors, tacrolimus and cyclosporine, drugs administrated during immunosuppressive treatment after kidney transplantation as an alternative to decrease the usage of corticosteroids. However, these medicines are not free of adverse effects.[5]

Secondary aHUS due to the intake of tacrolimus is rarer than cyclosporine. The syndrome initiated by the calcineurin inhibitors is explained based on the fact that they behave as glomerular constrictors, reducing the glomerular filtration rate, consequently raising the renal vascular resistance.[5]

The nephrotoxicity related to the calcineurin inhibitors is known since it began to be used in clinical practice, but its benefits in controlling the rejection of the graft outweighed the issues allied to the adverse effects. However, after it was observed that the morbidity related to these effects is considerably significant.[6]

There are some options of treatment to aHUS, which are eculizumab,[7] plasmapheresis and/or plasma infusion.[1] The patients presented earlier were treated with one of these.

Both plasma-based therapies, plasmapheresis and plasma infusion, guarantee replacement of normal levels of complement factor H (CFH), complement factor I (CFI), factor B and C3. However, only plasmapheresis is able to remove the mutated complement factors, as well as the autoantibodies against CFH.[4,7,8]

Eculizumab is a humanised monoclonal antibody that prevents the activation of C5 and formation of its anaphylotoxin, C5a, that can lead to the formation of the membrane attack complex (C5b-9) that mediates the end-organ inure in aHUS.[2] Therefore, it blocks pro inflammatory and pro thrombotic functions of complement system. The most serious adverse effect related to this medicine is the higher risk of meningococcal infections, which makes important that at least 2 weeks prior to therapy all patients should receive a meningococcal vaccine.[9]

Zuber et al. developed a prospective study of eculizumab, as an aHUS treatment, that included transplanted and no-transplanted patients. The results showed that this treatment has better efficacy than plasma-based therapy for either aHUS prevention or treatment.[9] These outcomes are a great advance when in comparison with the oldest records that present that more than two thirds of patients used to die or progress to terminal renal failure.[7]

Zuber et al. state that this treatment should be prescribed as a substitute to the plasma-based therapy for all the patients with aHUS due to the possibility of preventing the risks of complication related to central venous catheter, shortening the hospitalization time and periods of dialysis, and obtaining better renal function and consequently improving patient's quality of life.[9]

Legendre et al. analyze 37 patients with aHUS that were treated with eculizumab and the results were encouraging. There were evidences of efficient blocking of complement system activation, as the platelet levels enhanced and the number of microangiopathy thrombotic events decreased to zero. The renal function improved considerably, making it possible for patients of dialysis to suspend this therapy. The study also provided sufficient data to advocate that the sooner the intervention with the medicine, the better are the clinical benefits.[3]

Ruebner et al. disagree with the idea of delivering the same treatment for all the aHUS cases because of the variable prognosis of this disease. They discuss the importance of detailed analyses of each patient before prescribing both plasma-based therapy or eculizumab. Ruebner et al. mentione in his paper three situations of aHUS that did not have complement system mutations and were treated with plasma-based therapy for 3-4 weeks and obtained relief of symptoms, not presenting relapse throughout the period of follow up, 16-24 weeks. The high cost of treatment with eculizumab and the risks of morbidity and mortality related to the deficiency of complement system regulation lead. Ruebner et al. recommend this therapy only in the cases in which the patients have positive familial history of aHUS, recurrent aHUS, hypocomplementemia and patients that do not respond to plasmapheresis after 3 to 5 days.[10]

In conclusion, despite the fact that aHUS secondary to calcineurin inhibitors is a rare disease, it should be considered to the symptomatic patients that are intaking this medicine. It is a serious illness and therefore all patients with non-immune hemolysis and kidney alterations need to undergo an investigation through confirmatory exams so as to establish the proper therapy. Although the usage of eculizumab for treatment of the aforementioned affection is still recent, it already presents benefits in comparison to the plasma-based therapy that continues to be part of clinical practice. Because only a few case reports similar to the ones discussed in this paper are found in literature, they will certainly contribute to future studies and scientific evidences related to this area.

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