Síndrome Hemolítica Urémica e Infeção por SARS-CoV-2: Uma Associação Rara

Hemolytic Uremic Syndrome and SARS-CoV-2 Infection: A Rare Association

Cristiana Honrado Martins[1], José Damasceno Costa[2], Paulo Pereira[2], Ana Rita Matos[2], Vânia Gomes[2], Guilherme Castro Gomes[2]

Resumo:

As microangiopatias trombóticas (MAT) são doenças raras, com elevada morbimortalidade. Destas, a síndrome hemolíticaa urémica (SHU) atípica, associado à desregulação da via alternativa do complemento (genética/adquirida), representa um desafio diagnóstico. Caracteriza-se por microangiopatia trombótica, sendo a lesão renal aguda uma das principais características. A detecção de fatores etiológicos/precipitantes (*triggers* de MAT) é fundamental, ainda que 30% dos casos permaneçam idiopáticos. Não existe um teste diagnóstico direto, acabando este por ser um diagnóstico final de exclusão (tanto causas primárias como secundárias). A testagem de variantes genéticas é importante em termos prognósticos.

Descreve-se o caso de uma doente de 40 anos, cuja marcha diagnóstica culminou num SHU atípico associado à infeção pelo SARS-CoV-2, que se destaca pela raridade. Ressalva-se a importância do diagnóstico inicial célere e início atempado de tratamento efetivo dirigido: Eculizumab, único atualmente disponível em Portugal. A instituição de plasmaferese e/ou terapêutica de substituição renal devem ser consideradas individualmente.

Palavras-chave: COVID-10/complicações; SARS-CoV-2; Síndrome Hemolítica Urémica Atípica/diagnóstico; Síndrome Hemolítica Urémica Atípica/tratamento.

Abstract:

Thrombotic microangiopathies (TMA) are rare diseases, with high morbimortality. Among them, atypical hemolytic uremic syndrome (HUS), associated with deregulation of alternative complement pathway (genetic/acquired), represents a diagnostic challenge. Characterized by thrombotic microangiopathy, acute renal failure is one of its main features. Etiological/precipitant detection (TMA triggers) is essential, even though about 30% of cases remain idiopathic. There is not a direct diagnostic test, which makes this an exclusion final diagnosis (after primary and secondary causes are ruled-out). Further testing for genetic variations is important for prognostic purposes.

We describe the case of a 40 years old woman, whose final diagnostic was an atypical HUS associated with SARS-CoV-2 infection. This case stands out by its rarity.

We underline the importance of prompt initial diagnosis and timely target treatment beginning: Eculizumab, the only one available in Portugal at the moment. Plasmapheresis and/or renal replacement therapy must be considered case by case.

Keywords: *Atypical Hemolytic Uremic Syndrome/diagnosis; Atypical Hemolytic Uremic Syndrome/therapy; COVID-19/complications; SARS-CoV-2.*

Introduction

Thrombotic microangiopathies (TMA) are rare diseases, with high morbimortality.[1] Among them, hemolytic uremic syndrome (HUS) related to deregulation of alternative complement pathway, also known as atypical HUS (aHUS), represents a diagnostic challenge.[1,2]

We describe a case of aHUS associated with SARS-CoV-2 infection.

Case Report

A 40-years-old woman, with a medical history of left chromophobe renal cell carcinoma, submitted to left nephrectomy two months before admission, was admitted to emergency department of a local hospital with complaints of vomiting, diarrhea, oliguria and facial edema, with a four days evolution. She had a positive test for SARS-CoV-2 infection, five days before admission, classified as respiratory moderate disease (pneumonia without hypoxemia) and indication to ambulatory treatment.

Analytical tests were performed: blood panel showed anemia (hemoglobin: 8.7 g/dL), thrombocytopenia (platelet count: 16 000/mm^3), total leukocyte count of 6000/mm^3 and normal coagulation times; urea: 127 mg/dL, creatinine: 5.5 mg/dL, urinary sediment: 25 to 50 erythrocytes/field and proteinuria (urinary sediment proteins: 363 mg/dL); albumin: 2.9 g/dL; lactic dehydrogenase (LDH) > 1000 U/L, indoseable haptoglobin, negative Coombs' test and peripheral

[1]Serviço de Oncologia Médica, Hospital de Braga, Braga, Portugal
[2]Serviço de Medicina Interna, Hospital de Braga, Braga, Portugal

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blood smear showing schistocytes. This data revealed relevant acute renal failure (ARF) with proteinuria and microangiopathic hemolytic anemia (MHA).

Thoracic, abdominal and pelvic computed tomography (CT-TAP) and positron emission tomography (PET-SCAN) ruled out neoplastic recurrence.

Further TMA and ARF etiologic investigation revealed C3 complement consumption, without other positive findings: ADAMTS13 activity of 100%; negative *Escherichia coli* O157:H7 test; negative beta-hCG test; negative broad immunological study; normal methylmalonic acid (MMA) and methionine; negative infectious serologies; negative anti-factor H.

Therapy with plasmapheresis was performed until thrombotic thrombocytopenic purpura (TTP) exclusion, without further clinical and/or analytical improvement. The patient maintained oliguria, with difficult volume management (anasarca and recurrent right pleural effusion), leading to renal replacement therapy (RRT) with hemodialysis.

Genetic study revealed C3 heterozygous mutation and complement factor H (CFH) homozygous mutation. These results consolidated the main diagnosis of aHUS associated with complement deregulation, most probably triggered by SARS-CoV-2 infection.

Therefore, and while the patient was still in hospital internment, eculizumab treatment began,[2] with major clinical and analytical improvements (mainly in hematological alterations). Given the induced iatrogenic immunosuppression state, recommended vaccines were administered.

At this point, the patient was discharged, keeping strict follow-up in Day Care Unit, with clinical observation and analytical studies, followed by eculizumab administration. Six months after discharge, the patient remains asymptomatic, with MHA complete resolution and stabilized creatinine in a new base line of 3.5 mg/dL, allowing RRT suspension. Since then, no other intercurrence was registered.

Discussion

Thrombotic microangiopathies are rare diseases, with multiple etiologies, characterized by MHA (negative Coombs test) and thrombocytopenia. It usually presents with high morbimortality, directly related to endothelial lesion provoked by microthrombotic phenomena and subsequent target organ damage.[1,4] One of the recent TMA etiopathogenic classification subdivides primary TMA (including TTP and HUS, atypical and typical forms, the last one mainly in post-infectious and *Escherichia coli* productive Shiga toxin induced cases) and secondary TMA (induced by systemic disturbances, toxics, pregnancy, surgeries, among others).[1]

Hemolytic uremic syndrome is a systemic disease, characterized by thrombotic microangiopathy with endovascular affection, having the kidney as a particularly vulnerable organ. This way, ARF is one of its major features.[3,4] Nevertheless, extrarenal manifestations are present in about 20% of cases.[2]

Regarding atypical HUS, and unlike the so-called typical forms, there is a deregulation of alternative complement pathway, that can be either genetic or acquired.[4] A variety of clinical conditions (infectious, neoplastic, and immunological) and toxicologic exposures can act as TMA triggers. In case of positive genetic mutation, a trigger is also usually needed to disease development.[5] The presence of autoantibodies against complement activation inhibitors (among which complement anti-factor H autoantibody stands out) can produce similar phenotypes (acquired aHUS).[1,2]

In spite of all, about 30% of aHUS cases remain as idiopathic, with no trigger identification.[3] There is not a specific test to direct aHUS diagnosis,[1] which makes this a clinical and, essentially, an exclusion diagnosis.[2] It is possible to detect complement alterations in about 50% to 60% of cases.[6] In a first phase, diagnostic flow charts directed to TMA focus on TTP exclusion (ADAMTS13 activity quest: severely decreased in TTP) and Shiga toxin associated infectious HUS exclusion (E. coli O157:H7 quest). Simultaneously, secondary causes must be ruled out (pregnancy, surgical aggressions, immunological status evaluation, infectious serologies, methionine dosage). They can overlap aHUS, clinically and histopathologically.[1-5] Further testing for complement system genetic variations or other relevant autoantibodies (such as anti-factor H) is important in terms of prognostic.[2]

Atypical HUS target treatment is based on the blockage of complement inappropriate activation[1,2] and eculizumab (anti-C5 antibody) is the only effective treatment currently available in Portugal. The administration should begin as soon as possible,[1] representing a significantly positive prognostic factor. Even so, etiological and/or precipitating factors exclusion is essential since the beginning of clinical symptomatology, in order to correct target treatment initiation or, at least, to begin supportive care strategies (such as RRT). Starting empirical plasmapheresis must be considered after an initial diagnosis of unknown etiology TMA, especially given TTP prevalence and the poor prognosis associated with delays in plasmapheresis initiation in those cases.[1,2] Plasmapheresis should be maintained until TTP exclusion and suspended after that, since it is not effective on aHUS. Plasmapheresis and eculizumab should not be done simultaneously, since monoclonal antibody can be removed by plasmapheresis, decreasing its efficacy.

Once aHUS become the most probable diagnosis, eculizumab should be started.[1,2] The recommended dosing schedule for eculizumab in aHUs is reported in trials: an initial phase (900 mg every week for the first 4 weeks), followed by a maintenance phase (1200 mg for the fifth week and then 1200 mg every fourteen days).[2]

Recently, European Medicines Agency (EMA) approved ravulizumab (another anti-C5 antibody) in aHUS treatment.[7] However, this drug has not been approved for aHUS treatment in Portugal yet.

It is crucial to underline the importance of a prompt initial diagnosis. This will allow a timely target treatment beginning (prognostic factor and therapeutic response predictor). It is recommended treatment maintenance until platelet count normalization, hemolysis complete resolution and renal function sustained improvement. As seen in the described case, renal response can be slow, requiring an eculizumab trial of, at least, six months.[1,2] We highlight the importance of meningococcal infections prophylaxis, with prophylactic antibiotherapy and vaccination as recommended.[1,2] Eculizumab discontinuation must be approached and discussed with a multidisciplinary team, being a key and mandatory factor in these patients' follow-up.[2]

The reported case stands out by the rarity of HUS associated with complement deregulation and SARS-CoV-2 showing up as the most probable decompensation factor (association considering temporal link between events and the absence of other plausible alternatives). Atypical HUS and SARS-CoV-2 virus (infection/vaccination) association is rare, with only a few described cases in literature.[4,8-10] ■

Previous Presentations

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Declaração de Contribuição

CHM: Conceção do trabalho, rascunho do artigo e revisão crítica.
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Correspondence / Correspondência:

Cristiana Honrado Martins - cristiana.honrado.martins@hb.min-saude.pt
Serviço de Oncologia Médica, Hospital de Braga, Braga,
Rua das Comunidades Lusíadas 133, Braga

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