Atypical hemolytic-uremic syndrome (aHUS)

Gustavo Adolfo Domínguez-Ramírez, Paola María Blanco-Pertuz • Santa Marta (Colombia)
Guillermo Andrés Herrera-Rueda • Bucaramanga (Colombia)

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Abstract

Atypical hemolytic-uremic syndrome (aHUS) is a diagnosis of exclusion which should be proposed in cases where there is microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury. It is associated with mutations which cause dysregulation of the complement system and implies an adverse prognosis and a high risk of progression to chronic kidney disease. Following, we present the case of a patient with aHUS, highlighting the effect and importance of biologic therapy with the monoclonal antibody eculizumab. **(Acta Med Colomb 2019; 44. DOI: https://doi.org/10.36104/amc.2019.1301).**

Key words: *atypical hemolytic-uremic syndrome, complement activation, thrombotic microangiopathies, chronic renal failure, monoclonal antibodies.*

Dr. Gustavo Adolfo Domínguez-Ramírez: Médico General; Dra. Paola María Blanco-Pertuz: Médico General, Universidad del Magdalena. Santa Marta (Colombia). Dr. Guillermo Andrés Herrera-Rueda: Residente tercer año de Medicina Interna, Universidad Industrial de Santander. Bucaramanga (Colombia).
Correspondencia: Dr. Gustavo Adolfo Domínguez-Ramírez. Santa Marta (Colombia)
E-mail: gustavo.dr018@gmail.com
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Introduction

Atypical hemolytic-uremic syndrome (aHUS) is an infrequent entity characterized by the triad of thrombocytopenia, microangiopathic hemolytic anemia and acute kidney injury. It is a diagnosis of exclusion, ruling out Shiga toxin-producing *Eschericia Coli* (STEC) infection (usually serotype O157:H7, related to classic or typical hemolytic-uremic syndrome) and other secondary causes of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura (TTP). The annual incidence of aHUS is estimated to be two cases per million inhabitants in the United States, with a reported prevalence of 3.3 cases per million in patients under the age of 18 (1). The disease is more common in children under the age of 18 (60 vs. 40%), with a similar distribution between the sexes (2). In general, it has a poor prognosis, with a high risk of morbidity and mortality if not diagnosed and treated within the first year. In addition, approximately 65% of individuals will develop chronic kidney disease requiring dialysis within three to five years of diagnosis (3). It is thought that the pathogenesis of aHUS lies in a dysregulation of the complement system due to mutations of the genes which code its proteins, such as factor H, factor I, protein C3, and membrane cofactor CD46 (4). Beginning in 2011, the FDA approved the monoclonal antibody eculizumab as the treatment of choice for aHUS, significantly modifying the prognosis of these patients (5). Thus, this article emphatically explains the importance of maintaining a high index of suspicion in order to benefit the patients with the efficacy and safety of prompt initiation of biological therapy and thus avoid adverse outcomes.

Case presentation

A 40-year-old male patient was admitted due to a three-day history of approximately 10 liquid stools per day, nonbilious vomiting, diffuse abdominal pain, jaundice and facial edema. On the initial physical exam, he had the following vital signs: BP 210/123 mmHg, HR 112 bpm, RR 24 bpm, SpO2 88%, T 36.8°C, and Glasgow 13/15. He was encephalopathic with grade 3 edema in his lower extremities, abdominal ascites with wall edema, generalized crepitus, inter and subcostal retractions, markedly jaundiced conjunctivas and a history of anuria in the last two days. Parenteral management of the hypertension was begun with sodium nitroprusside, and he was given supplementary oxygen by nasal cannula and empiric broad-spectrum antibiotic treatment (meropenem plus vancomycin) due to suspected sepsis (3 points on Quick-SOFA). The admission paraclinical exams showed severe hemolytic anemia, given the presence of mixed hyperbilirubinemia, frankly elevated lactate dehydrogenase (LDH) and evidence of schistocytosis (++) on the peripheral blood smear (PBS). In addition, there was severe thrombocytopenia and significant elevation of nitrogen compounds, compatible with acute kidney injury (AKI) (AKIN 3) (Table 1). He was admitted to the intensive care unit (ICU) due to worsening oxygenation indices, where acute pulmonary edema in the interstitial phase was confirmed, and non-invasive mechanical ventilation was begun, with subsequent hemodialysis due to signs of uremia and fluid overload.

The patient persisted with severe bicytopenia despite transfusion therapy and pulses of methylprednisolone (1 gr IV every 24 hours). Polycultures and direct Coombs were negative, as well as IgM antibodies for dengue and

leptospirosis, with no evidence of blood parasites on a thick blood smear. Expansive diagnostic studies did not indicate autoimmunity (Table 2). Of note were diminished complement levels. Histopathology of the bone marrow showed adequate hematopoiesis of the three blood lines, without abnormal cell populations. A hematology consult considered that he would benefit from therapeutic plasma exchange, so he underwent 17 plasmapheresis sessions, with an adequate clinical response. An ADAMTS13 assay was performed to rule out TTP, with no evidence of enzyme deficiency (13.7% activity).

Given the foregoing, a medical committee of attending specialists in critical care, internal medicine and hematology determined that the patient fulfilled the diagnostic criteria for aHUS. Treatment was begun with eculizumab, 900 mg IV weekly for four weeks as the initiation phase, followed by 1,200 mg IV every 14 days as maintenance. He received the first dose in the hospital with a positive response, was discharged and continued outpatient treatment, with a marked reduction in hemolytic activity and recovery of the residual kidney function (Table 3).

Discussion

The prompt diagnosis of aHUS, with early initiation of biological treatment, is a challenge in the emergency context, given the high risk of progression to advanced chronic kidney disease. The simultaneous occurrence of non-immune microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury make up the diagnostic triad. Hemoglobin levels <10 g/dL, elevated serum LDH, a notable decrease in serum haptoglobin levels and the presence of schistocytes on the PBS, without a positive direct Coombs, confirm the anemic syndrome mediated by microangiopathic hemolysis (6). In addition, hypocomplementemia was seen in our case; however, this finding is not very sensitive or specific, being reported in only 30-50% of cases (7, 8). While it is true that the initial clinical picture of the patient in this case suggested infectious gastroenteritis, no enterobacteria were isolated. It should be emphasized that approximately 37% of individuals with aHUS may have gastrointestinal manifestations, often diarrhea (which may be bloody), nausea, vomiting, colitis and abdominal pain, which does not exclude the diagnosis (9,10). On the other hand, ADAMTS13 (plasma disintegrin) activity was not diminished, ruling out a diagnosis of TTP, which is characterized by less than 5% enzyme activity. A study of 214 patients with thrombotic microangiopathy showed that a severely low platelet count ($<30 \times 10^3/mm^3$) with serum creatinine <2.25 mg/dL was commonly found in 157 of 160 patients with severe ADAMTS13 deficiency, which suggests that kidney damage is usually not severe in TTP, with platelet deficiency being a more florid finding. This could be useful in differentiating it from aHUS (1, 11, 12).

Although plasma exchange was the main treatment method for managing aHUS since 1980, complement dysregulation and thrombotic microangiopathy persisted with this option, with a 65% rate of progression to advanced kidney disease during the first year after diagnosis, in spite of treatment (13). In contrast, the prognosis of patients with aHUS has significantly improved since the approval of

Table 1. *Admission labs.*

Lab test	Value (normal range)
Hemoglobin	4.5 (13.3-16.2 g/dL)
MCV	86.6 (79-93.3 fL)
MCH	32.2 (26.7-31.9 pg/cell)
RDW	16.2 (11.6-14.8%)
Platelets	45.3 (150-450 x $10^3/mm^3$)
Leucocytes	3.84 (3.55-10.50 x $10^3/mm^3$)
Total bilirubin	43.29 (0.25-1.28 mg/dL)
Direct bilirubin	25.79 (0.09-0.40 mg/dL)
Indirect bilirubin	17.49 (0.19-0.88 mg/dL)
LDH	5,980 (120-228 U/L)
Creatinine	8.8 (0.4-1.20 mg/dL)
BUN	119.9 (7-19 mg/dL)
ALT	61.8 (12-39 U/L)
AST	345.6 (7-42 U/L)
PT / INR	16.9 (12.7-15.4 s) / 1.34 (0.75-1.50)
PTT	32.3 (26.3-39.4 s)
Fibrinogen	401 (233-496 mg/dL)
PCR	4.82 (<10 mg/L)

Table 2. ***Autoimmune profile.***

Lab test	Value (normal range)
Antinuclear antibodies (ANAs) by IIF	Reactive 1/80
Anti-DNA antibodies by IIF	Non-reactive
pANCAs / cANCAs by IIF	Non-reactive
IgG antibodies / IgM anticardiolipin by ELISA	1.13 / 6.07 (0-15 U)
IgG antibodies / IgM anti-beta 2-glycoprotein by ELISA	1.03 / 0.68 (0-20 U)
IgG antibodies / IgM antiphospholipids by ELISA	Negative
Complement C3 fraction	42.1 (88-177 mg/dL)
Complement C4 fraction	36 (16-47 mg/dL)

Table 3. Follow-up labs at the end of the eculizumab initiation phase.

Lab test	Value (Normal range)
Hemoglobin	9.1 g/dL (13.3-16.2 mg/dL)
Platelets	137 (150-450 x 10^3/mm^3)
Total bilirubin	1.59 (0.25-1.28 mg/dL)
Direct bilirubin	0.89 (0.09-0.40 mg/dL)
Indirect bilirubin	0.69 (0.19-0.88 mg/dL)
LDH	624.6 U/L (120-228 U/L)
Creatinine	2.3 (0.40-1.20 mg/dL)
BUN	31.41 mg/dL (7 - 19 mg/dL)

eculizumab as the treatment of choice in 2011. Eculizumab is a monoclonal antibody which binds with high affinity to complement protein C5, preventing the terminal formation of anaphylatoxin C5a and the membrane attack complex (C5b-C9), thus inhibiting the proinflammatory and cytolytic effects of this system. The evidence suggests that after the initiation phase, the mean time for reaching a normal platelet count and serum LDH level was 7 and 28 days, respectively. Likewise, 75% of patients reached a hemoglobin level above 10 g/L in week 26 of treatment, and 80% of those who required renal replacement therapy and began treatment with eculizumab in the first month after diagnosis were able to discontinue hemodialysis, with a mean improvement in glomerular filtration rate (GFR) greater than 30 ml/min/1.73 m^2 at week 27 (14, 15). In our particular case, an increase of GFR up to 27.7 ml/min/1.73 m^2 was achieved approaching the first 30 days of treatment, with hemoglobin greater than 9 g/dL and a platelet count greater than $100 \times 10^3/mm^3$. Most patients tolerate this medication well, and it is recommended that patients be immunized against *Neisseria meningitidis*, *Streptococcus pneumoniae and type B Haemophilus influenzae at least two weeks prior to beginning the biological agent, given the increased susceptibility to encapsulated bacteria (16, 17).*

Conclusions

Eculizumab is a well-tolerated treatment which, when begun early, is associated with a significant reduction in thrombotic microangiopathy in patients with aHUS, producing a marked reduction in the rate of progression to chronic kidney disease and the need for dialysis. Thus, prompt detection by ruling out STEC infection and TTP is fundamental for positively impacting the serious morbidity and mortality associated with this syndrome.

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