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Case Report

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Post-staphylococcal atypical hemolytic uremic syndrome: A pediatric case report in a tertiary hospital

Síndrome hemolítica urêmica atípica pós-estafilocócica: relato de caso pediátrico em um hospital terciário

Síndrome hemolítico urémico post-estafilocócico atípico: reporte de un caso pediátrico en un hospital terciario

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ABSTRACT

Introduction: Atypical hemolytic uremic syndrome (aHUS) is a rare condition with potentially severe progression. It is classified as primary when caused by internal factors (such as genetic mutations) and secondary when triggered by external factors (infections, medications and toxins, autoimmune diseases, pregnancy, among others). **Objective:** To report a pediatric case of aHUS following *Staphylococcus aureus* infection in a tertiary care hospital. **Case description:** A previously healthy 1-year-and-9-month-old female presented with microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury secondary to *Staphylococcus* coagulase-negative infection. The diagnosis of aHUS was established based on characteristic laboratory findings and the exclusion of other causes, such as thrombotic thrombocytopenic purpura. The clinical course required intensive support, including multiple blood transfusions and peritoneal dialysis, culminating in recovery of renal function. **Discussion**: aHUS often has rapid clinical progression and is rare in the pediatric population. The combination of symptoms frequently necessitates dialysis and repeated transfusions. This case highlights the importance of considering uncommon infectious etiologies in aHUS and reinforces the need for early diagnostic and therapeutic intervention to reduce complications
Keywords: Atypical Hemolytic Uremic Syndrome; Thrombotic microangiopathies; Acute kidney injury; *Staphylococcus aureus*; Case report.

RESUMO

Introdução: A síndrome hemolítica urêmica atípica (SHUa) é uma condição rara, com possível evolução grave, sendo primária quando causada por alterações internas (mutações genéticas) ou secundária, quando desencadeada por fatores externos (infecções, medicamentos e toxinas, doenças autoimunes gestação, entre outras). **Objetivo:** Relatar um caso pediátrico de SHUa pós-infecção por *Staphylococcus aureus* em um hospital terciário. **Descrição do caso:** Paciente do sexo feminino, 1 ano e 9 meses, previamente hígida, apresentou anemia hemolítica microangiopática, plaquetopenia e lesão renal aguda secundária à infecção por *Staphylococcus* coagulase negativa. O diagnóstico de SHUa foi estabelecido com base em achados laboratoriais característicos e exclusão de outras etiologias, como púrpura trombocitopênica trombótica. A evolução clínica exigiu suporte intensivo, com múltiplas transfusões e diálise peritoneal, culminando em recuperação da função renal. **Discussão:** A SHUa evolui rapidamente na maioria dos casos, tendo pouca incidência em pacientes pediátricos. O conjunto de sinais e sintomas torna necessário a implementação de diálise e seriadas transfusões de hemocomponentes. Este caso destaca a importância de considerar etiologias infecciosas incomuns na SHUa e ressalta a necessidade de abordagem diagnóstica e terapêutica precoce para redução de complicações.
Palavras-chave: Síndrome hemolítica-urêmico atípica; Microangiopatias trombóticas; Injúria renal aguda; *Staphylococcus aureus*; Relato de caso.

RESUMEN

Introducción: El síndrome hemolítico urémico atípico (SHUa) es una enfermedad poco frecuente con progresión potencialmente grave. Puede ser primario cuando es causado por alteraciones internas (mutaciones genéticas) o secundario cuando es desencadenado por factores externos (infecciones, medicamentos y toxinas, enfermedades autoinmunes, embarazo, entre otros). Objetivo: Informar de un caso pediátrico de SHUa tras una infección por Staphylococcus aureus en un hospital de tercer nivel. Descripción del caso: Paciente femenina de 1 año y 9 meses, previamente sana, presentó anemia hemolítica microangiopática, trombocitopenia y lesión renal aguda secundaria a una infección por Staphylococcus coagulasa negativo. El diagnóstico de SHUa se estableció con base en los hallazgos de laboratorio característicos y la exclusión de otras etiologías, como la púrpura trombocitopénica trombótica. El curso clínico requirió soporte intensivo, con múltiples transfusiones y diálisis peritoneal, que culminó en la recuperación de la función renal. Discusión: El SHUa progresa rápidamente en la mayoría de los casos, con baja incidencia en pacientes pediátricos. La combinación de signos y síntomas requiere diálisis y transfusiones seriadas de hemoderivados. Este caso destaca la importancia de considerar etiologías infecciosas poco comunes en el SHUa y subraya la necesidad de un diagnóstico y tratamiento tempranos para reducir las complicaciones.
Palabras Clave: Síndrome hemolítico urémico atípico; Microangiopatías trombóticas; Lesión renal aguda; *Staphylococcus aureus*; Caso clínico.

INTRODUCTION

Hemolytic uremic syndrome (HUS) is a rare condition characterized by the classic triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.[1] It occurs most frequently in children under 5 years of age, with an incidence of 5 to 6 cases per 100,000 children per year, a value significantly higher than the global incidence estimated at 0.5 to 1 case per 100,000 inhabitants per year.[2]

HUS can be classified into two main forms. The typical form, responsible for approximately 90% of cases, is usually associated with infection by *Shiga* toxin-producing *Escherichia coli*. The atypical form (aHUS) corresponds to about 5% to 10% of cases and is related to genetic alterations as a primary cause or to secondary conditions that result in complement system dysfunction.[3]

In cases of aHUS, abnormal activation of the complement system leads to intensification of primary and secondary hemostasis. This process culminates in endothelial damage to the renal vessels and, consequently, in predominantly renal injury.[4] In adults, HUS usually manifests with general malaise and fatigue. In children, the picture may include pallor, tiredness, vomiting, lethargy, and other symptoms associated with the underlying disease.[5]

The diagnosis of aHUS is essentially clinical and is based on the exclusion of other causes of thrombotic microangiopathy, based on specific criteria. Among the differential diagnoses that should be ruled out are typical HUS, thrombotic thrombocytopenic purpura, genetic alterations, and secondary causes. Treatment is based on intensive clinical support and control of complement system activity.[6]

This work reports a rare and poorly documented case of aHUS triggered by staphylococcal infection, highlighting its clinical importance and challenging the traditional patterns associated with this condition. In addition to describing the clinical manifestations and the diagnostic process in detail, the study compares the patient's particularities with existing data in the literature.

The study was approved by the Research Ethics Committee, under protocol number 7.256.220, and followed the precepts of the CARE Guideline.

CASE DESCRIPTION

Female patient, 1 year and 9 months old, weighing 14 kg and measuring 0.85 cm, with no previous comorbidities, was admitted to the emergency department of a tertiary hospital, referred by SAMU (Mobile Emergency Care Service) and sent by a health unit from a neighboring municipality. She presented with persistent fever, prostration, and cough for five days. The previous day, a family member reported five episodes of hemoptysis. At the time of admission, she presented in fair general condition, moaning, afebrile, dehydrated, tachycardic (181 bpm), tachypneic (70 breaths per minute), decreased vesicular murmur in the right hemithorax, and other physical examinations within normal limits. Initial laboratory tests were requested, which demonstrated anemia (Hb 10.5 g/dL), thrombocytopenia (11,000 /mm³), and indirect hyperbilirubinemia (2.87 mg/dL) (Table 1). Chest X-ray showed consolidation in the right upper lobe and right pleural effusion (Figure 1). Supportive measures were performed, blood component transfusions were administered, and empirical antibiotic therapy was initiated with Ampicillin 1g injectable every 6 hours.

The patient's condition worsened, and she was transferred to the intensive care unit (ICU). Tests were ordered, which revealed the need for a new transfusion of red blood cells, platelets, and plasma. Ampicillin was replaced with Vancomycin 15 mg/kg every 6 hours and Cefepime 50 mg/kg injectable every 24 hours for 14 days. Further tests revealed a significant increase in creatinine (1.40 mg/dL) and urea (126 mg/dL) levels and a reduction in the estimated glomerular filtration rate (eGFR) (16.41 mL/min). After initial stabilization, thoracotomy and drainage of the pleural effusion were performed. Pleural fluid culture negative. At the end of the same day, the patient developed upper gastrointestinal bleeding, epistaxis, and ecchymosis all over her body.

On day 2, blood culture result was positive for

coagulase-negative *Staphylococcus*. Patient edematous (+2/+4) and oliguric, Furosemide 0.3 mg/kg every 8 hours was started. In the following two days, she remained anemic (Hb 8.2 g/dL) and with the presence of schistocytes, associated with thrombocytopenia (14,000 /mm³) and reduced eGFR (5.59 ml/min), requiring more blood transfusions. Furosemide was increased to 2.0 mg/kg every 8 hours with partial improvement of the volume overload condition (edema +2/+4 and urine volume 1.6 ml/kg/h).

On the 5th day of admission, the patient presented with anasarca, and acute kidney injury (AKI) was identified, classified as KDIGO 3 non-oliguric (creatinine 4.59 mg/dL with acute increase) and urea (359 mg/dL), requiring peritoneal dialysis. Antibiotic doses were adjusted to Vancomycin 10 mg/kg every 24 hours and Cefepime 50 mg/kg every 24 hours. Antibiotic therapy was discontinued on the 14th. The patient remained on dialysis until the 16th day of admission, showing normalization of volume status and serum potassium levels (K 3.8 mEq/L).

After 16 days of hospitalization and maintaining the symptoms of anemia, thrombocytopenia, and AKI, investigation for HUS and differential diagnosis of thrombotic thrombocytopenic purpura (TTP) was initiated. ADAMTS 13 dosage performed, result of 47%, confirmed aHUS.

On the 27th, she developed urinary tract sepsis with urine and blood cultures for multidrug-resistant *Klebsiella pneumoniae*. Antibiotic therapy was initiated with Amikacin 15mg/kg/day every 24 hours for 10 days. She remained in the ICU until the 30th, with resolution of the aHUS. Subsequently, she was transferred to the pediatric ward for eight days to monitor her overall condition. On the 38th, she was discharged home and referred for outpatient follow-up with replacement of ferrous sulfate 3 mg/kg/day. The patient was followed by nephrology and pulmonology services for the four months following hospital discharge. Given the absence of sequelae, she was discharged from the respective outpatient clinics. Currently, the patient is clinically stable. She remains under outpatient follow-up with pediatrics.

DISCUSSION

This report describes the case of a previously healthy patient who developed atypical hemolytic uremic syndrome (aHUS) following an infection caused by coagulase-negative *Staphylococcus*, an uncommon agent, especially in the pediatric age group. aHUS is a rare condition, with an estimated prevalence of 4.9 cases per million in individuals under 20 years of age, and an annual incidence between 0.26 and 0.75 per million in this age group.[6] The presence of the three classic signs – anemia, thrombocytopenia, and acute kidney injury – associated with rapid unfavorable clinical progression, emphasizes the severity and the need for early recognition in order to avoid future complications.

The secondary form of the syndrome presented by the patient accounts for about 5-10% of HUS cases in children. It differs from the typical form in that it is not related to infection by *Shiga* toxin-producing *Escherichia coli*. Its pathophysiology involves the dysregulated activation of the alternative complement pathway, with C3b deposition and formation of the membrane attack complex (C5b-9), resulting in endothelial injury, microvascular thrombosis, and intravascular hemolysis.[7,8] In this case, serum C3 levels were not measured, which limits the laboratory confirmation of this mechanism. In the context of *Staphylococcus* infection, the release of toxins and the intense systemic inflammatory response, with the production of cytokines such as IL-6 and TNF-α, can aggravate endothelial dysfunction. This process also potentiates complement activation, favoring the development of thrombotic microangiopathy.[9,10]

The patient initially presented with a lower respiratory tract infection with significant systemic repercussions, associated with hemoptysis, pulmonary consolidation, and pleural effusion. These findings motivated the medical team to make an initial diagnosis of complicated community-acquired pneumonia (CAP), which justifies empirical antibiotic therapy at first. Given the situation, the isolated use of ampicillin is not the most recommended by current Brazilian pediatric guidelines. In this

case of severe CAPC, initial empirical treatment with ceftriaxone or cefotaxime is recommended.[11]

The hematological evolution with severe anemia and schistocytes in the peripheral blood, thrombocytopenia, acute kidney injury, elevation of indirect bilirubin associated with the need for multiple transfusions, was decisive for the suspicion of thrombotic microangiopathy (TMA). The dysregulation of the complement system induced by the infectious agent results in continuous activation against antigens and cellular structures of the host. This exacerbated activation promotes intense platelet adhesion and aggregation in the renal microvasculature, culminating in the formation of thrombi and subsequent thrombocytopenia. In parallel, a picture of acute kidney injury develops. In the context of thrombotic microangiopathy, red blood cells that pass through obstructed capillaries undergo mechanical fragmentation, assuming the form of schistocytes.[12]

The differential diagnosis with thrombotic thrombocytopenic purpura (TTP) was performed by measuring ADAMTS 13 activity. The value of 47% ruled out the hypothesis of TTP (<10%) and supported the diagnosis of aHUS, according to clinical-laboratory criteria described in the literature.[7]

In the present case, the patient required multiple transfusions of blood components, use of diuretics and peritoneal dialysis, due to acute kidney injury with KDIGO 3 classification. The treatment of aHUS is based on intensive clinical support.[13] The use of eculizumab, a monoclonal antibody that blocks the cleavage of C5 and prevents the formation of the membrane attack complex (MAC), represents the main specific therapy.[6,7] The unavailability of this medication at the institution constituted a therapeutic limitation.

The prognosis for aHUS depends on early diagnosis, response to treatment, and associated complications. Studies indicate that the mortality rate is 5-25%, and 50% of cases develop end-stage renal disease during the acute phase.[4] This was not observed in the patient described, who has maintained resolution of the condition to date.

The correlation between the clinical findings and the current literature reinforces the consistency of the actions taken. Limitations inherent in case reports, such as the impossibility of generalizing the results, restrict the direct applicability of the findings to other populations. Future studies with a larger number of cases and expanded access to specific therapies may deepen the knowledge about aHUS, favoring the development of more precise diagnostic and therapeutic strategies.

The favorable outcome of the case, with recovery of renal function and monitoring of the hematological profile (Figure 2), reinforces the importance of a multidisciplinary approach, continuous surveillance, and early diagnostic suspicion in cases of hemolytic anemia with thrombocytopenia and renal injury, especially when associated with severe infections by poorly known agents.

This report contributes to the literature by reinforcing the still poorly described association between staphylococcal infection and the development of atypical HUS, highlighting the need for further investigation in similar clinical cases.

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Table 1. Laboratory results during clinical investigation

Laboratory tests	Tests ordered during hospitalization								
	D - 1	D - 2	D - 3	D - 4	D - 5	D - 14	D-16	D - 28	D-37
Blood count									
Hemoglobin (g/dL)	10.5	7.7	11.2	6.8	8.2	11.1	8.8	10	9.2	7.6
Hematocrit (%)	31	-	30.2	18.8	23.2	33.7	25.5	29.2	27.8	24.2
MCV (µm³)	81	-	-	-	-	-	80	-	-	-
Leukocytes (/mm³)	8010	7300	12960	13550	14940	28100	11270	8240	13540	12650
- Segmented (%)	73	46	59	58	65	75	64	55	63	50
- Rods (%)	-	6	20	10	8	9	1	1	-	1
- Lymphocytes (%)	20	29	16	20	16	9	22	35	-	-
- Monocytes (%)	7	7	3	10	9	4	12	9	-	7
Platelets (/mm³)	11.000	9.000	37.000	20.000	14.000	111.000	177.000	48.000	167.000	50.000
Kidney function									
Creatinine (mg/dL)	-	1.4	2.44	3.61	4.11	4.59	2.1	2.05	0.57	0.27
GFR (mL/min)	-	16.41	9.42	6.36	5.59	5.01	10.94	11.21	40.3	85.09
Urea (mg/dL)	-	126	202	283	342	359	93	92	28	10
Electrolytes									

Calcium (mEq/L)	-	1.12	1.22	1.27	-	1.24	1.15	1.13	1.19	-
Magnesium (mEq/L)	-		2.27	2.25	-	2.21	2.73	2.11	1.47	-
Sodium (mEq/L)	-	127	130	132	-	134	127	132	136	-
Potassium (mEq/L)	-	4.1	4.3	4.6	-	6.8	3.6	3.8	4	-
Liver biochemistry										
Total bilirubin (mg/dL)	-	3.26	-	-	-	-	1.05	-	-	2.36
Direct bilirubin (mg/dL)	-	0.39	-	-	-	-	0.49	-	-	1.27
Indirect bilirubin (mg/dL)	-	2.87	-	-	-	-	0.56	-	-	1.09
Blood gas analysis										
pH	7.26	-	7.33	7.2	7.13	6.96	7.38	-	7.41	-
pO2 (mmHg)	118	-	191.2	171.7	127.1	152.8	178.8	-	123	-
pCO2 (mmHg)	18	-	27.9	24.1	24.9	34.7	36.7	-	20	-
HCO3 (mmol/L)	7.9	-	14.8	9.7	8.4	7.9	21.7	-	12.9	-
ABE (mmol/L)	-16	-	-9	-16.6	-18.8	-22.8	-2.4	-	-8	-
Others										
CRP	-	>160	>160	101.2	64.8	70.1	33.5	-	29.2	28.6

Caption: MCV: Mean corpuscular volume. GFR: Glomerular filtration rate. BE: Base excess. CRP: C-reactive protein

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