Adult hemolytic uremic syndrome

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ABSTRACT

Hemolytic uremic syndrome (HUS), described in 1955, is characterized by the triad of non-immune mediated hemolytic anemia, thrombocytopenia, and acute kidney injury. Shiga toxin, produced most frequently by E coli O157:H, is involved in its pathogenesis.

Hus can manifest at any age, although it is rare in adults and develops sporadically or in outbreaks. HUS presents with a picture of abdominal pain, diarrhea, fever and vomiting. It can affect the central nervous system, lungs, pancreas, and heart.

In adults, the syndrome evolves after an incubation period of 1 week after diarrhea, with high morbidity and mortality, unlike pediatric cases.

We present the case of an adult patient who was hospitalized for hemolytic uremic syndrome.

Key words: diarrhea, adults, hemolytic uremic syndrome.

CASE PRESENTATION

A 64-year-old woman, a former smoker, is admitted with generalized abdominal pain of 3 days' duration. Twenty-four hours before admission, the patient added vomiting and bloody diarrhea. Her medical history included grade I obesity, arterial hypertension, dyslipidemia, hypothyroidism, and chronic obstructive pulmonary disease.

Laboratory tests showed: Leukocytosis 14,300 mm^3, Hematocrit 46.4%, Hemoglobin 15.5 g/dL, Creatinine 0.74 mg/dL, Uremia 22 mg/dL, Platelets 371,000 mm^3, Hyperamylasemia 18, CPK 99, LDH 264, Lactic acid 1.09 and Hepatogram without alterations.

A contrast-enhanced abdominopelvic CT scan showed segmental colitis at the level of the ascending and transverse colon (Fig. 1).

She started empirical antibiotic therapy with ceftriaxone and ornidazole on suspicion of infectious gastroenterocolitis. She completed seven days of antibiotics, tolerating the diet and decreasing bowel movements. The stool culture and parasitological examination of fecal material showed no relevant pathogens.

Seven days after admission, the patient presented non-oliguric acute renal failure (Fig. 2) and arterial hypertension that was difficult to manage, requiring three drugs for its control (enalapril, amlodipine, and lercanidipine). Laboratory tests showed anemia and thrombocytopenia not present on admission. Laboratory tests showed anemia and thrombocytopenia not present on admission. Given this situation, we proposed differential diagnoses of renal failure due to dehydration secondary to diarrhea; nephrotoxicity due to the drugs started, including interstitial nephritis due to antibiotics, and nephrotoxicity due to nonsteroidal anti-inflammatory drugs (NSAIDs).

The diagnosis of thrombotic microangiopathy rested on the evidence of anemia and thrombocytopenia accompanied by arterial hypertension (Fig. 3).

In this clinical context, a diagnosis of adult hemolytic uremic syndrome (HUS) gained relevance. The requested smear of peripheral blood showed 5% schistocytes. A 24-hour urinalysis showed proteinuria of 1.3 g/L.

A multiplex real-time polymerase chain reaction (PCR) test (FilmArray test) was performed on feces, with a *positive* result for *Shiga* toxin-producing *E. coli*.

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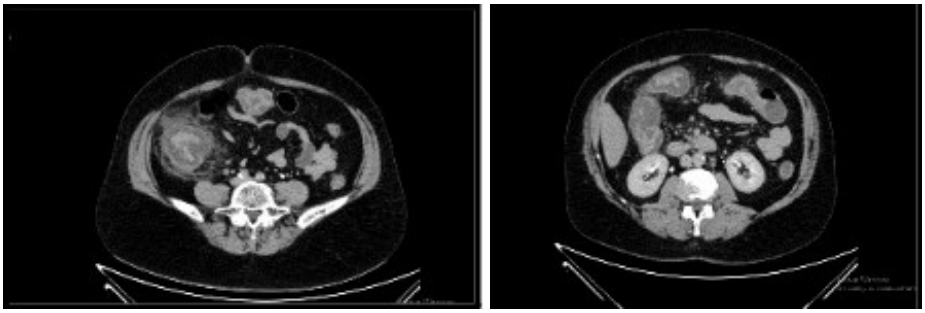

Figure 1. Computed tomography.

Days of hospitalizacion	Day 7	Day 14	Day 28	Day 35
Hemoglobin	11.1 g/dL	7.4 g/dL	9 g/dL	9 g/dL
Hematocrit	32.40%	21.10%	26%	26%/40%
Creatinine	1.58 mg/dL	2.82 mg/dL	3.26 mg/dL	2.02 mg/dL
Uremia	52 mg/dL	87 mg/dL	64 mg/dL	56 mg/dL
Platelets	90 000 mm^3	301 000 mm^3	440 000 mm^3	427 000 mm^3

Figure 2. Table of laboratory values in hospitalization.

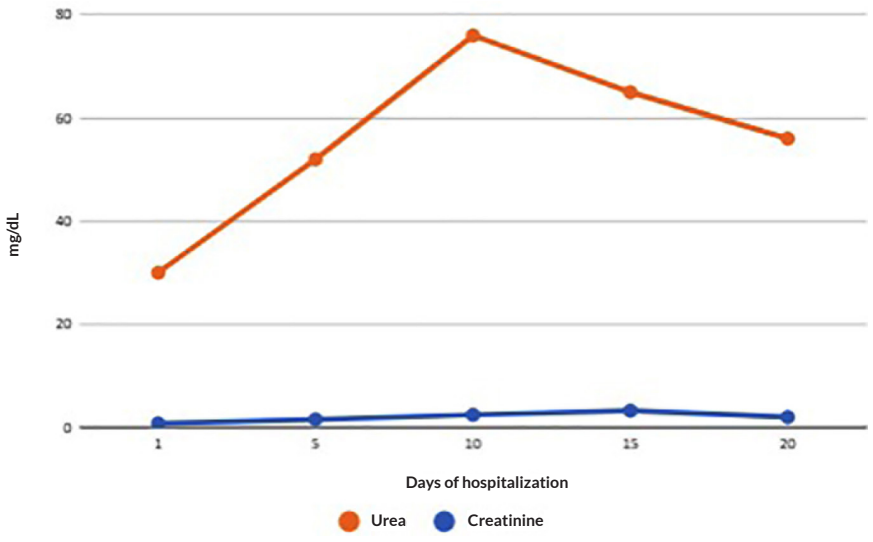

Figure 3. Evolution of renal function.

Given the clinical picture and the analytical and microbiological parameters, we arrived at a definitive diagnosis of an adult hemolytic uremic syndrome.

She started treatment with a comprehensive parenteral hydration plan, which evolved as clinically stable, decreasing hemolytic activity and improving renal function without requiring hemodialysis.

After 20 days she was discharged from the hospital with good subsequent clinical evolution. Two months after her discharge, laboratory tests showed normal hematocrit, platelets, and renal function. She also controlled arterial hypertension with monotherapy (amlodipine).

This study was performed under the guidelines of the modified Declaration of Helsinki.

DISCUSSION

Shiga toxin-producing Escherichia coli infection is an environmental disease transmitted by food or water, which causes bloody diarrhea. It is endemic in Argentina, as reported by the World Health Organization (WHO), and develops about 5000 infections a year. It is the first cause of renal failure in children and the reason for 20% of renal transplants in children and adolescents.

Approximately 5-20% of pediatric cases become complicated by the hemolytic uremic syndrome. The prevalence is much lower in adults, although precise data on this age group are lacking. In the winter of 1996, an outbreak of Shiga toxin-producing E. coli O157:H7 (STEC) occurred in Lanarkshire County, Scotland, resulting in 262 cases of bloody diarrhea, mainly in adults (79%, median 71 years), including 28 patients who progressed to HUS (11%), with sixteen deaths (57%)[1,2]. Shiga toxins can cause acute microvascular damage, leading to thrombotic microangiopathy (TMA), characterized by hemolytic anemia and thrombocytopenia; in HUS, it associates with acute kidney damage[3].

In children, HUS is the most frequent form of TMA and the primary cause of acute renal failure, while in adults, its incidence is lower and less studied.

In a retrospective study of 96 adults enrolled in a French cohort during 2009-2017, we observed a male-to-female ratio of 1:7 for this syndrome, with a median age of 60 years[4]. The characteristic clinical presentation of adult HUS begins with several days of severe abdominal pain and diarrhea, which becomes overtly bloody.

E. coli O157:H7 infections typically cause 1 to 3 days of non-bloody diarrhea, which becomes bloody afterward. That happens in about 90% of the cases and is usually the sign that leads to consultation.

E. coli O157:H7 infections have higher severity and mortality than conventional infectious diarrhea. In the French cohort mentioned above, mortality during hospitalization was 20%, while mortality in the Scottish cohort was 57%. It is worth noting that although the prevalence of HUS is higher in children, mortality is much higher in adults, especially after 60 years[5].

This diagnosis should be considered in patients with acute bloody diarrhea with severe abdominal pain, especially if they are fever-free.

Hospital admission, intravenous fluids, and transfusion support are recommended for severe anemia. Antibiotics, narcotics, non-steroidal anti-inflammatory drugs, and antispasmodics are not usually helpful.

The administration of antibiotics in Shiga toxin-producing E. coli (STEC) infections is controversial. It may depend on the infecting STEC genotype and the choice of antibiotic agent.

From clinical studies conducted in Japan during the 1996 Sakai outbreak in children, it was apparent that, in addition to the antibiotic administered, the timing of antibiotic administration seems to play a role in the progression of the infection until the development of HUS, as an early antibiotic may prevent the manifestation of HUS, while late antibiotic treatment may prevent its increase[6,7].

One study reported that fosfomycin decreased the incidence of HUS only if administered within the first two days of the disease. Delays in antibiotic administration lead to a gradual increase in incidence, depending on the day of initiation of the antibiotic treatment. In contrast to these results, we have reported that - while administration of trimethoprim-sulfamethoxazole (TMP/SMX) and b-lactams to STEC-infected children increased the risk of HUS - the risk is further increased if the antibiotics are administered within 72 hours after the onset of the illness[8,9].

In outbreak settings, prompt strain identification is possible through Whole-Genome Sequencing (WGS), which provides information on the serotype profile, virulence and resistance of the STEC isolate, following in silico analysis of the identified sequence. While this may offer guidance for antibiotic stewardship in epidemic settings, such information is not available in sporadic cases[10].

The differential diagnoses of this syndrome are: severe infectious diarrhea with acute renal failure due to hypovolemia, generally produced by enteropathogens such as Salmonella, Campylobacter, Yersinia, amebiasis, and Clostridium difficile. These can be confused with HUS; however, the diagnostic key will be thrombocytopenia and hemolytic anemia with schistocytes, which form a thrombotic microangiopathy (TMA).

In this diagnostic context, it is essential to rule out other causes of TMA, such as those produced in the last trimester of pregnancy (preeclampsia and HELLP), those produced by certain drugs such as calcineurin inhibitors, hematopoietic cell transplantation, severe infections with a systemic inflammatory response (catheter sepsis), patients with advanced metastatic cancer, certain patients with advanced collagenopathies such as systemic lupus erythematosus, and finally thrombotic thrombocytopenic purpura caused by antibodies against ADAMTS 13. The latter usually presents with ischemic neurological damage in most patients.

The other main differential diagnosis of HUS is intestinal ischemia, which predominates in elderly patients with established cardiovascular risk factors. While in intestinal ischemia, abdominal pain is sudden and prevails over diarrhea, HUS starts with progressive diarrhea and evolves with abdominal pain afterward.

CONCLUSION

In adults, HUS caused by Shiga toxin is a severe systemic disease that can cause multi-organ dysfunction.

The risk of death increases in persons older than 40, while young and middle-aged adults have clinical patterns similar to those seen in children.

The presence of bloody diarrhea associated with thrombocytopenia and microangiopathic hemolytic anemia must raise suspicion.

Careful questioning about the characteristics of abdominal pain will allow us to discern among its most important differential diagnoses, including intestinal ischemia, whose approach and treatment are different.

The rapid and specific etiological diagnosis of infectious diarrhea provides vital information for case management; multiplex PCR in stool samples is a method that allows the detection of a total of 22 pathogens among viruses, bacteria and parasites with minimal processing time. This technique is considered a highly satisfactory alternative for the detection of STEC.

The administration of antibiotics in infections caused by Shiga toxin-producing E. coli (STEC) strains, such as O157:H7, was and still is controversial.

Early antibiotic treatment could prevent the manifestation of HUS, provided that an appropriate agent is selected. It is recommended to avoid agents such as b-lactams and TMP/SMX in STEC infections, which increase the risk of HUS in all age groups, regardless of the timing of administration. Fosfomycin alone has been evaluated with some success in clinical settings.

In our patient, the conventional culturing did not provide enough sensitivity to diagnose. Worse symptoms after antibiotic administration were the key to raising the diagnostic suspicion, which we confirmed with multiple PCR. Early initiation of supportive treatment allowed a favorable clinical evolution.

Conflict of interest: the authors declare no conflicts of interest.

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