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Single Case

Campylobacter Colitis as a Trigger for Atypical Hemolytic Uremic Syndrome: About One Case

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Atypical hemolytic uremic syndrome · Campylobacter · Complement system · Alternate pathway

Abstract
We present the case of a 17-year-old Caucasian male whose condition featured acute renal failure, anemia, and deep thrombocytopenia after five consecutive days of diarrhea. *Campylobacter coli* was identified in stool cultures and, although the direct role of this germ in the pathogenesis of hemolytic uremic syndrome (HUS) remains uncertain to this day, initial presentation was considered broadly consistent with typical HUS. However, the patient showed no signs of spontaneous recovery over time. While secondary investigations showed no abnormalities in ADAMTS13 activity or in the alternate pathway of complement, patient's condition deteriorated. Worsening kidney failure required emergency renal replacement therapy and was followed by cardiac involvement in the form of acute heart failure. Given this unfavorable development, blood samples were drawn to look for mutations in the alternate complement pathway, and eculizumab therapy was initiated without further delay, allowing prompt improvement of cardiac function and recovery of diuresis. Upon discharge, the patient still had to undergo intermittent dialysis, which would later be withdrawn. Genetic analysis ultimately confirmed the presence of a complement factor H mutation associated with a high risk of disease recurrence, indicating long-term continuation of eculizumab therapy.

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Introduction

Hemolytic uremic syndrome (HUS) belongs to the family of thrombotic microangiopathies (TMA). The diagnosis of HUS is suggested by the following triad: mechanical hemolytic anemia, thrombocytopenia, and acute renal failure. In general, two types of HUS are distinguished: typical HUS, usually caused by Shiga toxin-producing *Escherichia coli* (STEC), and atypical HUS (aHUS) caused by deregulated complement activation. Here, we present the case of a 17-year-old adolescent with factor H-associated aHUS, whose initial presentation was that of a typical diarrhea-associated HUS. The purpose of this article was to draw attention to this peculiar onset of aHUS and to stress the importance of analyzing the alternate pathway of complement if the course of a supposedly typical HUS turns out to be unusual.

Case Report

A 17-year-old Caucasian male with no previous medical history presented to the pediatric emergency department on February 24, 2020, with a 5-day history of diarrhea. Interrogation revealed that the initially watery stools had turned bloody after 3 days. On the fourth day, vomiting and reduced food intake were added to the symptoms. After 5 days, the patient and his parents consulted their general practitioner, who prescribed a blood workup as well as a stool culture. Blood tests revealed acute renal failure (serum creatinine 3.6 mg/dL), thrombocytopenia (platelet count 15 G/L), and signs of mechanical intravascular hemolysis (hemoglobin 12.4 g/dL, bilirubin 48 mg/L, haptoglobin below 0.2 g/L, schizocytes at 0.4%). Upon questioning, the patient reported eating frozen chicken nuggets 2 days before the onset of symptoms. He was referred to the pediatric emergency department by his attending physician for suspected HUS.

On arrival at the pediatric ward, the patient weighed 66 kg for a height of 187 cm (BMI 18.9 kg/m^2). He had no fever, hemodynamic and respiratory status were stable. Urine output was preserved, with persistent macroscopic hematuria. Clinical examination revealed abdominal pain in the periumbilical region without signs of peritoneal irritation, as well as cutaneous and conjunctival jaundice. There was no organomegaly or lymphadenopathy. The rest of the examination was unremarkable. Abdominal ultrasound revealed bowel wall edema suggestive of colitis while stool cultures, performed a few days earlier at the patient's local laboratory, came back positive for *Campylobacter coli*.

Antibiotic therapy with azithromycin was initiated for a total of 5 days. Control stool cultures carried out upon admission (prior to antibiotic therapy) did not reveal STEC infection and Shiga toxin (*Stx*) gene PCR detection from fecal samples was negative. Patient received intravenous fluids whose composition and flow rate were adjusted to water intakes/losses and the evolution of plasma ionogram. Therapeutic management included close monitoring of fluid balance, body weight, and blood pressure. Several transfusions were necessary given the worsening anemia. Indeed, follow-up blood work showed severe mechanical hemolysis with 9% schizocytosis and a drop in hemoglobinemia to 6.1 g/dL, as well as deep thrombocytopenia (5 G/L at the lowest). A total of 7 units of packed red blood cells were administered. Patient's course over the first 10 days was overall favorable, marked by the regression of jaundice and digestive symptoms and an increase in platelet count to 60 G/L – although kidney failure was persistent.

Digestive symptoms briefly recurred, prompting the resumption of azithromycin at day 11 for a total of 3 days – which resulted in rapid improvement. Over the next 4 days, patient developed peripheral edema later associated with clinical pulmonary overload as urine

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output decreased (150 mL per day, i.e., 0.1 mL/kg/h) and creatinine peaked at 13.5 mg/dL. Moreover, there was no further improvement in platelet count, anemia was persistent and control stool cultures were negative. At this point, investigations did not show any abnormalities in ADAMTS13 activity or in the complement system: total complement activity, C3, C4, factor H, and factor I were normal, and the test for anti-factor H antibodies was negative. Follow-up abdominal ultrasound showed diffuse peritoneal effusion despite regression of bowel inflammation. Chest X-ray confirmed left pleural effusion of moderate abundance, associated with bilateral peribronchovascular thickening and upper lobe vascular redistribution. Weight then reached 72.5 kg (i.e., weight gain of 6.5 kg since admission).

Faced with this pejorative development, the patient was transferred to the intensive care unit (ICU) at day 17 to initiate continuous venovenous hemodiafiltration. Continuous intravenous calcium channel blocker therapy (nicardipine) was introduced in the context of severe arterial hypertension and subsequently continued orally (amlodipine). Progressive normalization of hematological parameters began from day 32 and allowed transfusions to be stopped (2 more units of packed RBC had previously been administered). By day 38, hemoglobinemia was within range on erythropoietin therapy and platelet count was over 200 G/L. Despite these improvements, the patient developed acute heart failure after 4 weeks in the ICU: cardiac ultrasound on day 39 indeed revealed left ventricular ejection fraction (LVEF) lowered to 30% as well as low volume pericardial effusion. Serum N-terminal pro-brain natriuretic peptide reached 34,194 pg/mL. MRI confirmed marked ventricular dysfunction in the context of hypertrophic cardiomyopathy with concentric remodeling of the left ventricle. In this context, amlodipine was replaced by an angiotensin-converting enzyme inhibitor (ramipril), and a beta-blocker was introduced (bisoprolol). There were no signs of myocarditis (notably no elevated troponins) and COVID-19 PCR testing was negative. Both autoimmunity and vitamin deficiency assessments were unremarkable. In parallel, there was no sign of recovery of renal function. Given the impossibility of withdrawal from dialysis associated with severe cardiac impairment, eculizumab therapy was initiated at day 41 on the advice of the referral center for TMAs, despite the absence of confirmed alternate complement pathway disorder. In parallel, blood samples were drawn to look for mutations in the alternate complement pathway proteins. Infusions were given weekly during the first month. All vaccinations were updated and antibiotic prophylaxis with oracillin was implemented prior to the first infusion. Heart function gradually improved within 15 days of treatment initiation. On the other hand, persistent anuria led to the establishment of long-term vascular access and to the performance of a renal biopsy on day 52, to both rule out possible differential diagnoses and assess the prognosis for recovery.

Upon histological examination, some glomeruli displayed mesangiolysis (Fig. 1a). Double contours were observed in Jones staining. Interstitial fibrosis was minimal (less than 5%) with mild diffuse edema and no noticeable inflammation. Some tubular sections exhibited hematic cylinders or flattened epithelial cells. Vascular examination revealed circumferential intimal cellular proliferation in small arteries (Fig. 1b) and important mucoid intimal thickening (Fig. 1c). A total of 38 glomeruli were visible, with sequelae of TMA complicated by tubular necrosis. Upon recovery of diuresis on day 55, the patient was transferred back to the pediatric ward and switched to intermittent dialysis (after 6 consecutive weeks on continuous venovenous hemodiaadhere to colonicfiltration). During his stay in the ICU, the patient had remained hemodynamically stable and without need for oxygen therapy or any respiratory support. The patient was discharged 2 weeks after leaving intensive care. He was then on dialysis three times a week and still received regular erythropoietin treatment. Creatinine remained elevated, around 4.2 mg/dL after the long (2-day) interdialytic interval. The evolution of plasma parameters between admission and discharge from intensive care is shown in Figure 2. One-month follow-up cardiac ultrasound

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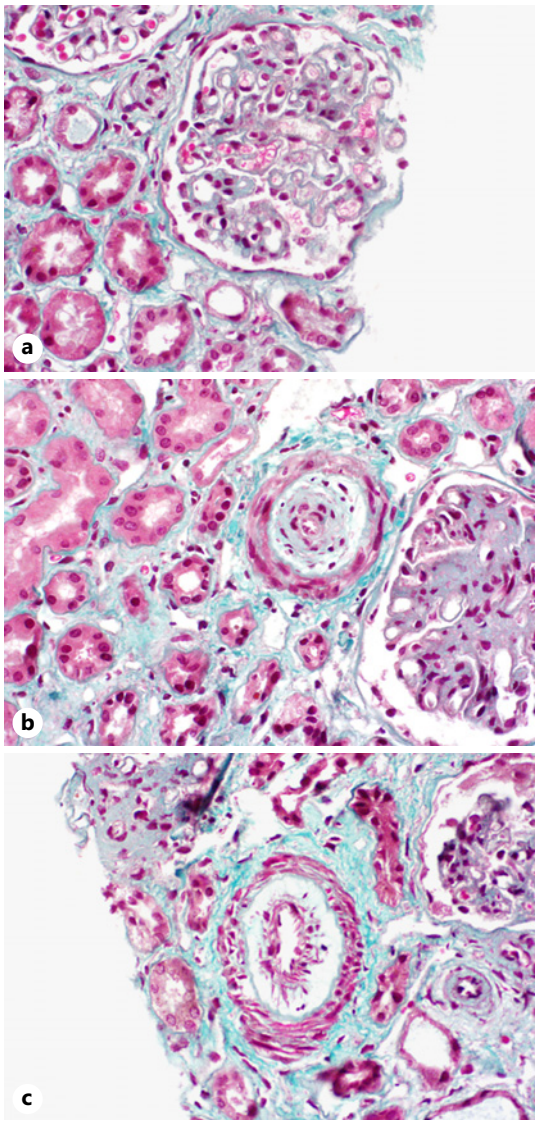

Fig. 1. a–c Representative histological sections.

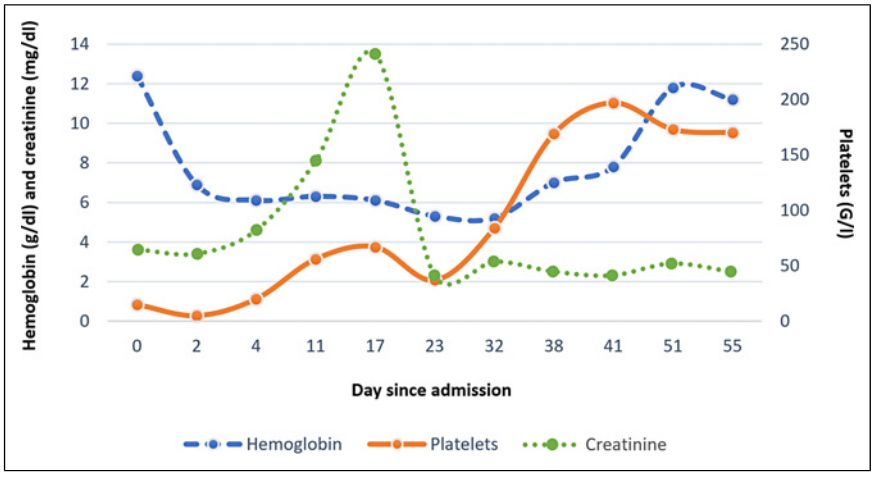

Fig. 2. Evolution of plasma parameters between admission and discharge from intensive care.

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showed improvement of ventricular function, with LVEF at 60%. It was decided to continue eculizumab therapy (every 2 weeks after the first month) until genetic investigations were obtained.

As the patient reached the age of majority, subsequent follow-up was provided in an adult nephrology department. Kidney function evolved favorably, allowing withdrawal of hemodialysis after 3 months of renal replacement therapy. The patient consulted 2 months after withdrawal, while still on eculizumab every 2 weeks. Blood pressure was well controlled with an ACE inhibitor and clinical examination revealed no signs of pulmonary or peripheral fluid overload. Plasma creatinine was 2.7 mg/dL, which corresponded to a GFR of 33 mL/min, and blood work showed no evidence of hemolysis. Follow-up ultrasound confirmed normalization of cardiac function with 64% LVEF and regression of pericardial effusion. The patient was seen again 3 months later, upon receipt of genetic analysis which showed a mutation of the factor H gene. The patient and his family were duly informed of the nature of this mutation affecting a key regulator of the alternate complement pathway, with a high risk of recurrence indicating long-term continuation of anticomplement C5 monoclonal antibodies. To this day the patient has not presented any recurrence of TMA on eculizumab, which is otherwise very well tolerated, and GFR has stabilized at around 40 mL/min.

Discussion

Hemolytic uremic syndrome (HUS) is characterized by a triad including mechanical hemolytic anemia, thrombocytopenia, and acute renal failure. Endothelial injury is key to its pathogenesis. Typical HUS, also referred to as diarrhea-associated HUS (D + HUS), usually occurs following digestive infection with *Stx*-producing *E. coli*. STEC adheres to colonic mucosal villi and release *Stx*, which binds to the receptor Gb3 (globotriaosylceramide) on endothelial cells [1]. Subsequently internalized by endocytosis, *Stx* causes endothelial cell injury by halting protein synthesis, resulting in platelet activation with intravascular thrombosis and mechanical hemolysis. In aHUS on the other hand, it is chronic and uncontrolled activation of the alternate complement pathway that plays a key role in endothelial damage [2, 3]. In this case, gene mutations in complement regulatory proteins are involved. The case we report here is challenging on several counts. First, although presenting as a typical diarrhea-associated HUS, stool cultures did not show STEC infection, and *Stx* gene PCR detection was negative – which begs the question of the direct cause-and-effect relationship between Campylobacter species and renal TMA. Second, it raises awareness among practitioners about the importance of exploring the alternate complement pathway in front of an unusual development. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000529941).

Cause-and-Effect Relationship between Campylobacter Species and HUS

As explained by Smith and Gunther [4] in their commentary on the topic, no Campylobacter strain that possesses a homolog to any known Stx-producing gene has yet been identified. A different pathogenesis could be hypothesized, such as that of pneumococcal HUS. It has been postulated that the Thomsen Friedenreich (TF) antigen – an antigen that is part of the surface of erythrocytes, platelets, and glomerular endothelial cells – is involved in the induction of HUS during invasive pneumococcal infection. *Streptococcus pneumoniae* neuraminidase A cleaves the layer of neuraminic acid in which the TF cryptantigen is concealed. Preformed host IgM antibodies then bind this newly exposed antigen, leading to endothelial injury [5, 6]. However, such neuraminidase activity has not been demonstrated in Campylobacter. Another possibility is that patients presenting with symptoms caused by STEC infection are actually coinfected with

another enteropathogen. Ardissino et al. [7] have shown that up to 39.9% of children with bloody diarrhea caused by STEC are coinfected with Campylobacter or Salmonella. Thus, a number of presumed non-STEC typical HUS cases might really be STEC-associated. Indeed, the absence of STEC strains by the time stool cultures are performed does not exclude their initial involvement – especially if the presence of Stx has not been sought. Consequently, to date, any direct role for Campylobacter in the pathogenesis of HUS remains to be demonstrated.

Campylobacter as a Trigger to the Onset of aHUS

Smith and Gunther [4] studied all cases of HUS in the literature reported to be due to Campylobacter infection since 1982. Out of eleven reports, only two (Carter and Cimolai, 1996 [8]; Soper et al., 2000 [9]) indicated that STEC strains were not found. In 2013, Kavanagh et al. [10] discussed the case reported by Carter and Cimolai of an acute *Campylobacter upsaliensis* gastroenteritis-associated HUS, suggesting that *C. upsaliensis* infection had probably triggered aHUS. However, since the presence of a mutation in complement regulatory proteins could not be confirmed in their patient, this assumption remains uncertain. By contrast in this case, genetic analysis confirmed the existence of a mutation of the factor H gene. To the best of our knowledge, this is the first reliable report implicating Campylobacter-induced colitis as a trigger for aHUS in a highly genetically predisposed individual.

Statement of Ethics

Ethical approval is not required for this study in accordance with national guidelines. Written informed consent for publication of the details of their medical case and any accompanying images was obtained directly from the patient, who had reached adulthood before the writing of this case report began.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Thomas Quinaux, Zead Tubail, Isabelle Vrillon, and Benjamin Savenkoff collected the data. Thomas Quinaux reviewed the relevant literature and wrote the manuscript. Hervé Sartelet provided photographs and carried out the analysis of histological sections. Isabelle Vrillon and Benjamin Savenkoff supervised the project.

Data Availability Statement

All data underlying the results are available as part of the article and no additional source data are required. Further inquiries can be directed to the corresponding author.

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