CASE REPORT

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Atypical Presentation of Shiga Toxin Haemolytic Uremic Syndrome (STEC-HUS)

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ABSTRACT

Shiga-toxin producing *Escherichia coli* (STEC) infection is the most common cause of haemolytic uremic syndrome (HUS) in children. It should be noted that 5% of STEC-HUS patients have no prodromal diarrhoea, while it may be present in up to 30% of atypical HUS (aHUS) cases. In patients at risk for aHUS, STEC infection may act as a trigger rather than playing a causative role. Presently, eculizumab is the first-line therapy for children presenting with aHUS, whereas treatment of children with STEC-HUS is mainly supportive. We report the case of a child with STEC-HUS who had a severe presentation, requiring renal replacement therapy in the acute phase and surgical treatment for a colonic stricture that arose as a late extra-renal complication of the disease. We aim to review the diagnostic workup of children presenting with HUS, stressing the resources available in our setting. In Portugal, O157 *E. coli* isolation medium is widely available in clinical laboratories. Non-O157 STEC identification requires specific testing, which is increasingly relevant as non-O157 STEC is becoming a more common cause of STEC-HUS than serogroup O157. The National Health Institute Doutor Ricardo Jorge (INSA) has the capacity to identify verotoxin genes and to proceed to verotxin-producing *E. coli* (VTEC) pathogenicity assessment using multiplex polymerase chain reaction. Fresh stool samples must be obtained early in the disease course to be sent for culture in O157 *E. coli* isolation medium and for non-O157 *E. coli* identification assays.

Keywords: Child; Eculizumab; Escherichia coli Infections; Hemolytic Uremic Syndrome Shiga-Toxigenic Escherichia coli

INTRODUCTION

Shiga-toxin producing *Escherichia coli* (STEC) infection accounts for the majority (>90%) of haemolytic uremic syndrome (HUS) cases in children. It affects mainly children under five years of age. In Europe, the annual incidence is 1.9 cases per 100 000 children aged three to five years and 0.5 per 100 000 among those aged 15 to 18 years.[1,2] In most cases (85%-90%) of STEC infection, haemorragic colitis resolves with no sequelae within one week. However, HUS may develop in 10%-15% of children infected with STEC, usually two weeks after the colitis onset. Nearly 40% of patients with STEC-HUS require renal replacement therapy.[3,4] Although rarely, extra-renal manifestations may occur, not only in the acute phase but also in the following months. Management of STEC-HUS is mainly supportive. While eculizumab, an anti-C5 monoclonal antibody, has been established as first-line therapy in HUS associated with disease-causing mutations in complement genes,[5,6] the role of complement blockade therapy in STEC-HUS remains unclear. It has been used in patients with STEC-HUS, especially in those with severe presentation and extra-renal manifestations, but evidence to support this is lacking. Therefore, the aetiological diagnosis of HUS has critical treatment implications.

Thrombotic microangiopathy (TMA) is a pathological description characterized clinically by the occurrence of thrombocytopenia, microangiopathic haemolytic anaemia (Coombs negative), and organ injury. It has traditionally been classified into HUS and thrombotic thrombocytopenic purpura (TTP), usually associated with predominant kidney injury in the former, and neurologic involvement in the latter. To further support the distinction, TTP is associated with "a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13" (ADAMTS13) activity below 10%, as a result from either a congenital or acquired decrease or absence of this protease. In the past, HUS had been divided into diarrhoea-positive and diarrhoea-negative HUS, also referred to as typical and atypical HUS (aHUS), respectively. Later, as the causal role of complement dysfunction has been recognized in a subgroup of patients with HUS the term "complement-mediated HUS" has emerged.[5] Therefore, considerable heterogeneity is found in the literature regarding the definition of aHUS, which can either refer specifically to complement mediated disease or more broadly to any TMA other than TTP and STEC-HUS.

Newer classifications replicate our increasing knowledge about the pathophysiology, including the genetic background and aetiologic

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triggers. In brief, TMA are currently classified into: primary, either inherited (e.g., complement mutations, *ADAMTS13* mutations, cobalamin C type (cblC) deficiency mediated TMA) or acquired (e.g., factor H autoantibodies, ADAMTS13 autoantibodies); secondary (e.g., TMA associated with autoimmune conditions, malignancy associated TMA, drug induced TMA, glomerular disease associated TMA, gene encoding diacylglycerol kinase ε (*DGKE*) TMA); infection-associated (e.g., STEC-HUS, pneumococcal HUS); or unexplained.[5-7]

Presently, aHUS is mainly (although not solely) a diagnosis of exclusion. In agreement with the most recent literature, we will reserve the term aHUS to cases in which TTP (i.e., ADAMTS13 activity <10%), infection (e.g., STEC infection, pneumococcal infection), other coexisting disease/condition better explaining the clinical picture, and underlying complement-independent genetic causes of HUS had been ruled-out.

Herein, we report the case of a child with STEC-HUS who had a severe presentation, requiring renal replacement therapy in the acute phase and surgical treatment for a colonic stricture that arose as a late extra-renal complication of the disease. We aim to review the diagnostic workup of children presenting with HUS highlighting the resources available in Portugal.

CASE REPORT

A previously healthy 4-year-old girl presented with non-bloody diarrhoea, colicky diffuse abdominal pain, and low-grade fever. There were no known epidemiological links to other cases. She was admitted to her local hospital on day three of illness, when diarrhoea became bloody. Initial laboratory workup was unremarkable (haemoglobin 13.3 g/dL [reference 11.5 - 13.5], 13 000 leucocytes/uL [75% neutrophils], platelets 190 000/uL [reference: 200 000 – 450 000], creatinine 0.42 mg/dL [reference 0.20 - 0.43], estimated glomerular filtration rate (eGFR) 131 mL/min/1.73 m^2, urea 26 mg/dL [reference: 15 - 36], PCR 1.9 mg/dL [reference <5.0]). Haemolysis screening was not ordered initially. At the time of admission, intravenous fluid therapy was started and partial improvement in general status was noted. Despite that, severe abdominal pain persisted. Early consultation with a paediatric surgeon helped rule out surgical causes of acute abdomen at that point. Abdominal ultrasound showed extensive colitis of the sigmoid and descending colon. No pathogen was identified in blood, urine or stool cultures. Specifically, no O157 *E. coli* was isolated from feces cultured on sorbitol MacConkey agar medium. Abrupt general deterioration occurred on day six of illness. Diarrhoea had resolved the day before, and no new evidence of rectal bleeding had been reported. The patient became pale and tachycardic, showing progressively worsening oliguria, oedema of the eyelid, and stage 2 hypertension (blood pressure was 134/85 mmHg, more than 12 mmHg above the 95th percentile for age, sex and height). The first blood samples taken on that day were consistent with haemolytic anaemia (haemoglobin 9.3 g/dL, alanine aminotransferase (ALT) 78 U/L [reference: 9 - 25 U/L], aspartate aminotransferase (AST) 204 U/L [reference: 21 - 44 U/L], lactic dehydrogenase (LDH) 2475 U/L [reference: 192 - 321], and schistocytes on a blood smear), thrombocytopenia (58 000 platelets/uL/uL), and acute kidney injury (creatinine 0.72 mg/dL [eGFR 76 mL/min/1.73 m^2], urea 71 mg/dL), leading to the diagnosis of HUS. Urinalysis was positive for haemoglobin, haematuria, and proteinuria (clear yellow urine, specific gravity 1.011, pH 6, protein 100 mg/dL, haemoglobin 0.10 mg/dL, 539 erythrocytes/uL). Urinary sediment was not performed. Laboratorial reassessment twelve hours later documented rapid deterioration (haemoglobin 6.9 g/dL, ALT 332 U/L, AST 220 U/L, LDH 3374 U/L), thrombocytopenia (40 000 platelets/uL), serum creatinine 1.75 mg/dL (eGFR 31 mL/min/1.73 m^2), and urea 100 mg/dL). Urine protein-to-creatinine ratio was increased (5.9 mg/mg) and an ultrasound revealed enlarged hyperechogenic kidneys. Coagulation tests were normal (thrombin time 12.0 seconds [reference: 10.6 - 12.1], activated partial thromboplastin time 30.0 seconds [reference: 26 – 36], D-dimer 753 ug/L [reference: <500], and fibrinogen 3.4 g/L [reference: 1.57 - 4.00]). Direct and indirect antiglobulin tests were negative. ADAMTS13 activity was normal (0.72 UI/mL [reference ≥0.67]). The patient was transferred to a tertiary hospital and admitted to the paediatric intensive care unit (PICU). The physical exam was remarkable for fluid overload and painful abdominal distension. The later, associated with leukocytosis 17 000/uL and an acute rise in C-reactive protein to 41 mg/dL, prompt the initiation of empiric treatment with ceftriaxone and metronidazole to cover sepsis from complicated intra-abdominal infection. Abdominal ultrasound continued to show marked oedema of the sigmoid and descending colonic wall, and ascites. On the first day in the PICU, respiratory distress in the setting of fluid overload (estimated in 17% from previous body weight) led to the need for mechanical ventilation support and veno-venous continuous hemodiafiltration (HDFVVC). The patient had been anuric for 12 hours at the time of HDFVCC initiation, despite diuretic therapy with furosemide in high-dose boluses (2 mg/kg/dose once and 5 mg/kg/dose twice). Eculizumab was considered at this point, given the rapid and severe renal and haematological deterioration, and taking into consideration that sedation for mechanical ventilation would limit the neurologic clinical examination. Meanwhile, verocytotoxin (*stx1*, *stx2*) and pathogenicity (*eae*) genes were detected on feacal samples collected at PICU admission and sent to the National Health Institute Doutor Ricardo Jorge (INSA), using multiplex polymerase chain reaction. Consequently, the diagnosis of STEC-HUS was confirmed and a decision to keep supportive treatment was made. Later on, a missense heterozygous variant in the *C3* gene (c.4855A>C, p.Ser1619Arg) was identified by next-generation sequencing. It was classified as "likely benign" according to the ACMG/AMP criteria (BP4; BP6; BS1)(8) and ranked as "tolerated" (score 0.05) using the rare exome variant ensemble learner (REVEL) meta-predictor.[9] Successful discontinuation of HDFVVC was possible after eleven days. Packed red blood cell transfusions were needed for four times during the first fourteen days in the PICU, followed by sustained haematologic recovery. Gastrointestinal involvement, however, took longer to resolve. Non-bloody diarrhoea resurged on the second week and lasted for another three weeks. Abdominal distension and pain persisted throughout her hospital stay, with no relevant findings on serial image studies other than the already described extensive colitis. Several multidisciplinary meetings with paediatric surgery, gastroenterology, and infectious disease team took place for regular reassessment of the best approach. A decision was made towards conservative management. In brief, the patient was treated with piperacillin-tazobactam, gentamicin, metronidazole, and liposomal amphotericin b. First exposure to antibiotics occurred at the time of transferal to the PICU after acute kidney injury had been clearly established. Progressive resolution of the clinical and laboratorial findings of colitis were seen in the

following three weeks. Despite improvement, signs of mesenteritis persisted on the abdominal ultrasound, which were assumed to be residual, with no other significant findings on image. The patient was discharged home after 17 days in PICU and another 30 days in the ward. At discharge, blood pressure was normal without medication, there was no evidence of haemolysis, haemoglobin was 11 g/dL, platelet count was 340 000/uL, serum creatinine was 0.40 mg/dL (eGFR 138 mL/min/1.73 m^2), and the urinalysis was unremarkable.

One month later, she presented with mild SARS-CoV-2 infection with no signs of HUS relapse. She was readmitted one month after COVID-19, for subacute abdominal occlusion. Abdominal computed tomography revealed a 2 cm stenotic segment between the descending and the sigmoid colon, which was clearly seen on contrast enema. Through laparotomy, resection of a hard mass made up of adhesions between the descending colon and adjacent structures was performed, exposing a stenotic segment. A segmental resection with primary anastomosis was performed. Pathology examination of the surgical specimen confirmed the presence of a stenotic segment with perforation, marked mixed inflammatory infiltrate, chronic transmural ischaemic wall changes, and necrosis. Postoperatory recovery was uneventful and the patient was discharged home.

Presently, at one-year of follow-up after HUS, the patient remains asymptomatic, looks healthy, has been growing and developing well, has normal blood pressure readings, normal complete blood count, no signs of haemolysis, normal serum creatinine, normal urinalysis, and an urine albumin-to-creatine ratio of 21 ug/mg.

DISCUSSION

Bloody diarrhoea in our patient suggested STEC-HUS. However, it should be noted that 5% of STEC-HUS patients have no prodromal diarrhoea.[5] Despite being more commonly associated with enteric infections, STEC-HUS may follow a urinary tract infection. Additionally, not all patients with potential disease-causing mutations in aHUS associated genes develop HUS. Diarrhoea or gastroenteritis is present in up to 30% of aHUS cases,[5] in which STEC infection may act as a trigger for aHUS rather than playing a causative role. A relapsing course in a patient initially assumed to have an infection-associated HUS strongly supports the trigger hypothesis. Critical appraisal of the genetic testing results is key to further differentiate STEC-HUS from aHUS triggered by STEC infection. Thus, STEC infection should be actively sought in any patient presenting with possible STEC and/or HUS, regardless of patient age, season of the year, or the presence or absence of blood in the stool. Stools should be tested as early as possible in the course of illness as the Shiga toxin genes might be lost and the likelihood of identifying STEC infection decreases over time, being almost impossible after one week. In certain circumstances, recovering plates from cultures obtained earlier in disease course that were not initially evaluated for STEC might be helpful.[10] Somatic (O) and flagellar (H) antigens in STEC define the O-serogroup and O:H-serotype. Routine stool cultures identify *Campylobacter*, *Salmonella* and *Shigella* spp. Specific procedures are needed for both O157 and non-O157 *E. coli* isolation and identification. *E. coli* O157:H7 is indistinguishable from most commensal *E. coli* on traditional lactose-containing media. Nevertheless, it can usually be distinguished from other *E. coli* by their inability (or delayed capacity) to ferment sorbitol. Lactose is replaced by sorbitol in sorbitol-MacConkey agar, making it the medium of choice for *E. coli* O157 isolation. It should be noted, however, that most non-O157 STEC strains ferment sorbitol and are not commonly isolated in sorbitol-MacConkey agar,[10] as our case illustrates. According to the European Centre for Disease Prevention and Control Annual Report from 2019, serogroup O157 was the most commonly reported serogroup associated with STEC infections, although the proportion of non-O157 serogroups has been increasing. Notably, serogroup O26 has been a more common cause of HUS than serogroup O157 since 2016.[11] All these data stress that stools from patients presenting with HUS should be simultaneously sent for culture in O157 *E. coli* isolation medium and for non-O157 *E. coli* identification assays.[10,12] In Portugal, sorbitol-MacConkey agar for O157 *E. coli* identification is widely available across most clinical laboratories and INSA has the capacity to identify verotoxin genes and to proceed to verotxin-producing *E. coli* (VTEC) pathogenicity assessment, which is key to the diagnosis of non-O157 STEC infection. In general, stool samples are preferable to rectal swab samples whenever possible. Bacteria isolated from stool cultures at local clinical laboratories should also be sent to INSA for additional testing.[6]

Extra-renal manifestations occur in up to 20% of children presenting with SETC-HUS. Acute gastrointestinal involvement usually manifests as bloody diarrhoea. More rarely, severe abdominal pain and/or distention, bowel ischaemia, necrosis, and perforation may also occur. Severe abdominal pain or acute abdomen in a child with STEC-HUS may indicate bowel ischaemia and/or perforation. These complications may be severe enough to require surgical intervention. Pathology studies of surgical specimens of children with STEC-SHU who underwent partial bowel resection have shown areas of oedema, haemorrhages, inflammatory infiltrate, and intestinal cell necrosis.[13] All the colonic segments of the bowel may be affected with the rectum being less frequently involved, although rectal prolapse has been described in series of children with STEC-SHU. Transmural necrosis of the colon may lead to subsequent colonic stricture. Despite its rarity, other case reports of colonic stricture occurring in children a few months to years after the acute episode of HUS have also been published.[14,15] Therefore, a diagnosis of intestinal obstruction should be considered in all children with a previous history of STEC-HUS presenting with constipation and abdominal distention.

The severity of the clinical presentation and the inability to identify a pathogenic strain of *E. coli* on the initial laboratory workup led us to proceed to genetic testing. The genetic variant identified in our patient (NM_000064.4(C3):c.4855A>C (p.Ser1619Arg)) was classified as likely benign. Although it has been reported in at least 10 individuals with aHUS, in nine being the sole variant, its prevalence in the European population is not statistically different from the prevalence in aHUS.[16] This variant is present in 0.2% (278/129 150) of European alleles including one homozygote, suggesting a benign nature.[17] Our patient completely recovered blood counts and renal function with supportive management, supporting the diagnosis of STEC-HUS. Additionally, HUS did not relapse after SARS-CoV-2 infection, also a trigger for aHUS, further supporting the benign nature of the variant.[18] Although pathogenic complement variants with minor allele frequency <0.1% were found more frequently in STEC-HUS patients from a French cohort (three out of 75, 4%) versus European controls (four out of

503, 0.8%), there was no significant correlation between the identification of a pathogenic variant and end-stage kidney disease (ESKD) at last follow-up.[19] To date, available data do not support a systematic genetic screening for patients presenting with post-diarrhoea HUS. However, genetic testing should be considered when STEC infection is believed to act as a trigger to unmask a complement deficiency, such as in patients with a fulminant course, progression to ESKD within 3 years, a family history of HUS, relapse of HUS, or post-transplant recurrence.[19] In children presenting with a first episode of HUS, genetic screening should be ordered after confirmation that there is no causative disease, no STEC infection, no severe ADAMTS 13 deficiency, and no hyperhomocysteinemia/methyl-malonic aciduria.[20]

There are no published data from randomized controlled studies to inform the optimal treatment for children with STEC-HUS. Plasma exchange has been used in children with severe STEC-HUS, especially in those with neurologic impairment, based on observational reports of favorable responses in adult patients.[21] The rationale for this is a theoretical assumption that plasma exchange could have a beneficial effect removing proinflammatory factors or even Shiga toxin from the circulation. Most evidence to date, however, does not support a role for plasma exchange in STEC-HUS. Accordingly, the American Society for Apheresis does not recommend plasma exchange for STEC-HUS, due to the lack of efficacy or potential for harm.[22]

There is increasing evidence suggesting a role for complement activation in the pathophysiology of STEC-HUS, although the exact mechanisms involved are not completely understood. Observational data from patients with STEC-HUS have shown increased plasma levels of alternative pathway activation products. STEC is capable of producing two Shiga toxins – *stx1* and *stx2*. Laboratorial studies have shown that *stx2* binds to complement factor H (CFH) impairing complement regulation on the cell surface. Additionally, decreased levels of CD59 mRNA, a regulator of the membrane attack complex, in glomerular endothelial cells treated with *stx2* suggest that it may contribute to terminal complement pathway dysregulation. Likewise, up-regulation of P-selectin on the surface of human microvascular endothelial cells (HMEC-1) co-incubated with *stx2* has been shown to activate C3, promoting microthrombi formation. All these possible mechanisms support complement activation in STEC-HUS pathogenesis.[23]

Eculizumab is a monoclonal humanized anti-C5 antibody, which prevents C5 cleavage and the formation of the membrane attack complex (C5b-9). Therefore, it inhibits the C5a pro-inflammatory and C5b-9 pro-thrombotic effects. It is the first-line treatment option for children with a clinical diagnosis of aHUS. If possible, eculizumab treatment should be initiated within the first 24 to 48 hours of HUS onset, while awaiting for the pending results.[20] The effect of one dose may last for two weeks with an acceptable safety profile, making early treatment appealing also in the setting of STEC infection, while the workup to differentiate true STEC-HUS from aHUS triggerd by STEC is still incomplete. Few studies have addressed the role of eculizumab in children with STEC-HUS, and the interpretation of their results is difficult to generalise considering the observational nature of the studies and the lack of a control group.[24,25] The results of the ongoing paediatric trials "Eculizumab in Shiga-toxin Related Hemolytic and Uremic Syndrome Pediatric Patients – ECULISHU" and "Eculizumab in Shiga-toxin producing *E. coli* Haemolytic Uraemic Syndrome – ECUSTEC" may help answer the question about the role of eculizumab in the treatment of children with STEC-HUS.

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