Case Reports

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Hemolytic uremic syndrome following complicated appendicitis in a child: what is the missing link?

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Abstract

We herein describe an 18-month-old boy who underwent initially successful surgical and antibiotic treatment of complicated appendicitis with postoperative occurrence of hemolytic uremic syndrome (HUS). This complication was due to Shiga toxin-producing *Escherichia coli* (STEC) found secondarily in rectal swabs but not in the peritoneal cavity. The literature indicates that a causal link may exist between these two entities, and HUS could be considered an iatrogenic complication of appendicitis management due to a multimodal stress effect in non-symptomatic STEC carriers.

Keywords

Hemolytic uremic syndrome, Shiga toxin, children, appendicitis, surgery, case report, *Escherichia coli*

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Introduction

Appendicitis is the most common surgical emergency in children, with an incidence of 1 per 1000 and a peak at approximately 10 years of age.[1] Most cases are due to isolated appendiceal infections with digestive aerobic bacteria such as *Escherichia coli* or *Klebsiella pneumoniae*.[2] In some cases, specific bacteria[3] or even viruses are isolated.

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In children aged <5 years, appendicitis is often complicated by perforation, abscess, and peritonitis because of a delayed diagnosis, secondary or nonspecific presentation, difficulty in communication, or symptoms that overlap with other pediatric illnesses.[4]

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy characterized by thrombocytopenia, hemolytic anemia, and kidney failure due to Shiga toxins from Shiga toxin-producing *E. coli* (STEC).[5] There is currently no specific treatment for this rare entity.

The diagnosis and management of HUS can be a dilemma for the pediatric surgeon[6] because the clinical presentation of HUS may be indistinguishable from that of acute surgical diseases of the abdomen, such as appendicitis or postoperative complications.[7] Actual surgical complications due to STEC species such as *E. coli* O157:H7 are very uncommon.[8] The relationship between the type of appendicitis and the development of HUS has not yet been clearly identified. Several cases of perforated appendicitis with secondary HUS,[8] and vice versa,[9] have been reported. Several cases of appendicitis with[8] or without a perforated appendix[10] have also been associated with the presence of *E. coli* O157:H7 but without HUS development.

We herein describe an 18-month-old boy who underwent surgical treatment of peritonitis and developed secondary HUS. The bacteriological analysis identified two microorganisms: a non-enteropathogenic *E. coli* found in the peritoneal cavity during the appendectomy and a STEC in the stools. The aim of this report is to highlight the link between peritonitis and the occurrence of typical HUS. Is it logical to expect a causal link between appendicitis and HUS?

Case report

An 18-month-old boy was referred to our emergency department with abdominal pain and a 2-day history of fever despite amoxicillin treatment for suspected otitis. He had no bloody diarrhea. He had no medical history, and all of his other family members were healthy.

Physical examination revealed a temperature of 38°C, abdominal bloating, and tiredness. A computed tomography scan indicated appendicitis (Figure 1). Blood examination revealed an inflammatory syndrome with a high C-reactive protein level of 236 mg/L (reference range, <5 mg/L). His blood cell count was 9.42×10^9/L (reference range, $4.5–14.5 \times 10^9$/L) with 75% neutrophils, his hemoglobin level was 9.5 g/dL, and his platelet count was 252 G/L.

The patient was managed in the operating room of the emergency department. Acute appendicitis with perforation was found at laparotomy. Postoperative intravenous antibiotic therapy with gentamycin, cefotaxime, and metronidazole was initiated. The initial postoperative sequelae were straightforward. The intraoperative swabs recovered wild-type *E. coli* with false membranes, *Clostridium ramosum*, *Bifidobacterium* spp., and *Bacteroides thetaiotaomicron*. The abdominal silicone drainage tube was removed on postoperative day 4.

The patient developed a persistent fever and progressive abdominal bloating on postoperative day 2. A computed tomography scan revealed peritoneal effusion in the right iliac fossa and parietal wall (Figure 1) on postoperative day 6. After a multidisciplinary discussion, redo surgery was performed to exclude a surgical complication. Twenty mL of pus were evacuated from the abdominal wall on day 7, and the antibiotic therapy was switched to piperacillin/tazobactam (Tazocilin™; Pfizer, Paris, France). Wild-type *E. coli* was found in the pus specimen of the parietal wall. Biological tests the day after the redo surgery revealed thrombocytopenia (platelet count of 35 G/L), hemolysis and

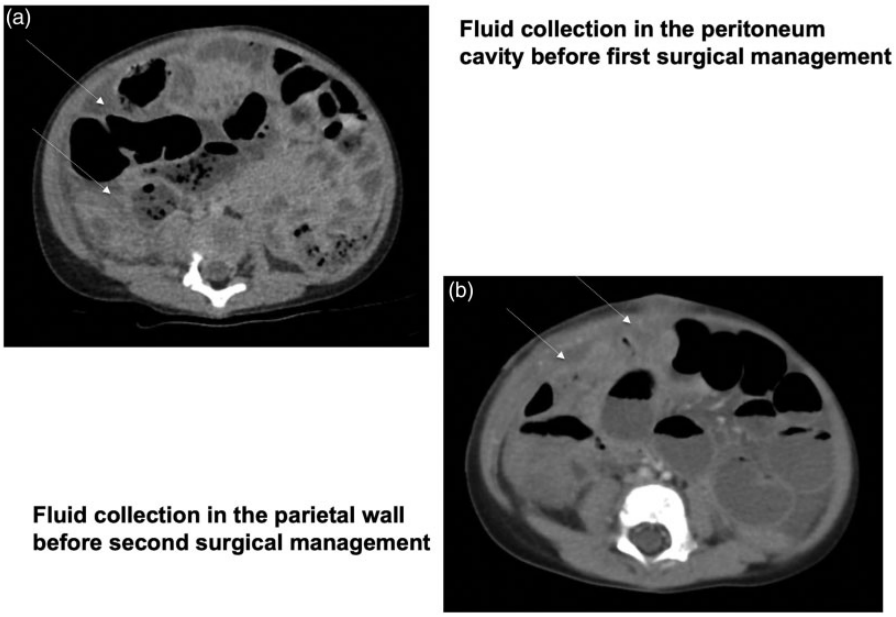

Figure 1. Abdominal computed tomography scan before surgery. (a) Fluid collection was present in the peritoneum (arrow) before the first surgical procedure. (b) An abscess was present in the parietal wall before the second surgical procedure.

nonregenerative anemia (hemoglobin of 8.9 g/dL, the presence of schistocytes, collapsed haptoglobin, and high lactate dehydrogenase of 1967 IU/L [reference range, 180–430 IU/L]), and renal failure (serum creatinine of 73 μmol/L [reference range, 15–31 μmol/L]). STEC was suspected and the patient was admitted to the intensive care unit for monitoring. The diagnosis was confirmed by rectal swabbing, which revealed the presence of *E. coli* with Shiga toxin Stx-2.

A water compensation was performed for the zero input/output balance sheet, and the antibiotic therapy was bolstered by the addition of azithromycin. The patient's subsequent clinical course was favorable, and he was discharged 10 days after the redo surgery. Tazocilin™ was continued for a total of 7 days. Both of the patient's brothers (3 months and 3 years of age, respectively) were positive for the Shiga toxin *eae*, and the older brother was also positive for Stx-2; however, both were asymptomatic. Azithromycin was administered to the older brother for 5 days.

Discussion

The identification of *eae* or Stx-2 Shiga toxin in patients with HUS associated with appendicitis has been described in a small number of case reports in the literature, but a clear link has yet to be made between these two entities.

Most published cases refer to atypical HUS. Reported risk factors for typical HUS include other stress conditions such as burn injuries[11] and the post-partum period.[12] Acute appendicitis is rare in children under 3 years of age and often presents with a deceptive clinical picture. The diagnosis is often delayed, resulting in a high

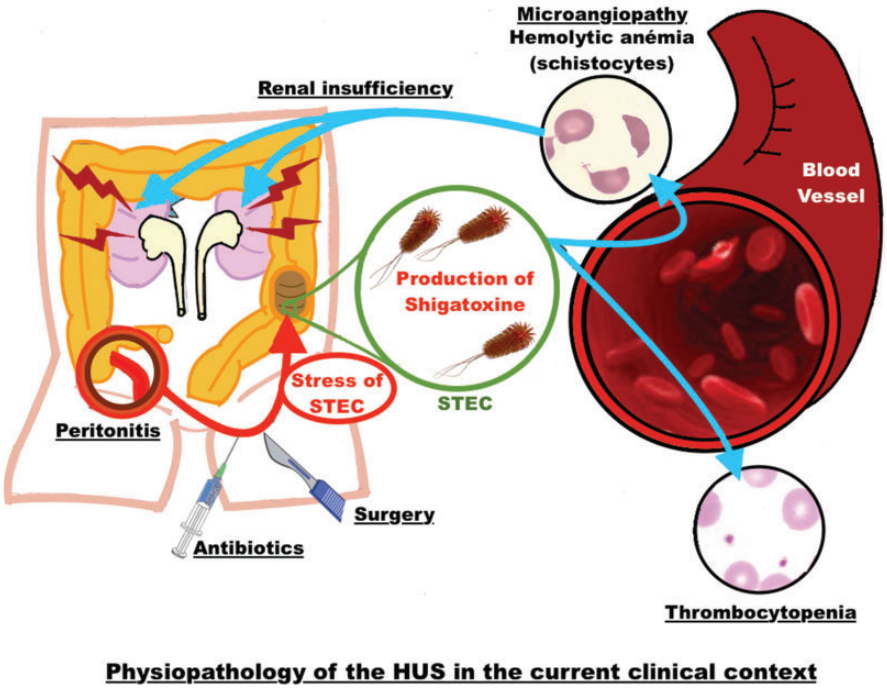

Figure 2. Pathophysiology of the hemolytic uremic syndrome after peritonitis in our patient. STEC, Shiga toxin-producing *Escherichia coli*.

rate of appendicular perforation (>80%).[1] In our case, the patient had complicated appendicitis with no obvious pathogenic bacteria. During the first operative management, wild-type *E. coli* was identified in the peritoneal fluid; it was also identified in the parietal abscess during the redo surgery. No STEC was found in the perioperative samples. Our hypothesis of asymptomatic prior presence of STEC in this patient is based on the presence of the same STEC in the patient's two young brothers.

The presence of certain bacteria in the microbiota in conjunction with the use of antibiotics influences the patient's susceptibility to STEC infection and increases the risk of typical HUS. The intestinal microbiota of healthy individuals normally has the ability to repress the expression of virulence factors. There are many variants of Stx-2 with different STEC strains that could exhibit pathogen and contamination diversification.[13] In our case, the patient's young age and thus intestinal immaturity was a risk factor for HUS occurrence.[13]

Antibiotic therapy increases the risk of HUS occurrence,[14] given the presence of *E. coli* O157:H7 in the intestinal tract. The addition of gentamycin during the first surgical management may have placed a degree of stress on the bacteria. Bactericidal antibiotics such as gentamycin are more likely to give rise to the development of HUS than are bacteriostatic antibiotics.[14] In vitro data have shown that *E. coli* O157 cultured with gentamycin produces more Stx Shiga toxin than does *E. coli* O157 alone.[15] This stress probably allows for acquisition of the Stx-2 gene by transduction with phages[16] and might explain the occurrence of the HUS symptoms 48 hours after the first surgery in

our patient. One study showed that an increase in temperature can also induce phages when associated with other inducers.[17] Antibiotic treatment of STEC is still a matter of debate, although azithromycin appears to be the most effective agent.[18] Azithromycin is thought to be able to inhibit Stx-stimulated cytokine production by human peripheral blood mononuclear cells and monocytes.[18] The efficacy of azithromycin against STEC has been demonstrated in mice.[19] In contrast, ciprofloxacin treatment has been shown to increase stress and the production of Stx.[20] The survival rate of affected neonatal pigs treated with azithromycin was higher than that of ciprofloxacin-treated animals and untreated controls.[21]

Thus, in summary, this case of typical HUS was probably an adverse effect of the antibiotic treatment and the stressful context of the peritonitis management (Figure 2). The risk factors were the patient's young age and adjunction of bactericidal antibiotics. When children develop postoperative thrombocytopenia with schistocytes, HUS should be suspected. Detection of STEC in stools is warranted for diagnosis, and the administration of azithromycin may favor rapid recovery.

Ethics and consent

Written informed consent for publication was obtained from the patient's parents. The requirement for ethics committee approval was waived because of the nature of this study (case report).

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Authors' contributions

All of the authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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References

1. Holcomb GW, Murphy JP and St Peter SD. *Holcomb and Ashcraft's pediatric surgery*. 7th ed. Amsterdam: Elsevier, 2019, pp.549–556.
2. Lob SH, Badal RE, Bouchillon SK, et al. Epidemiology and susceptibility of Gram-negative appendicitis pathogens: SMART 2008-2010. *Surg Infect (Larchmt)* 2013; 14: 203–208.
3. Arda IS, Ergin F, Varan B, et al. Acute abdomen caused by Salmonella typhimurium infection in children. *J Pediatr Surg* 2001; 36: 1849–1852.
4. Almaramhy HH. Acute appendicitis in young children less than 5 years: review article. *Ital J Pediatr* 2017; 43: 15.
5. Wong CS, Jelacic S, Habeeb RL, et al. The risk of the hemolytic-uremic syndrome after antibiotic treatment of Escherichia coli O157: H7 infections. *N Engl J Med* 2000; 342: 1930–1936.
6. Smith CD, Schuster SR, Gruppe WE, et al. Hemolytic-uremic syndrome: a diagnostic and therapeutic dilemma for the surgeon. *J Pediatr Surg* 1978; 13: 597–604.
7. Edmonson MB and Chesney RW. Hemolytic-uremic syndrome confused with acute appendicitis. *Arch Surg* 1978; 113: 754–755.
8. Cimolai N, Blair GK, Murphy JJ, et al. Impact of infection by verotoxigenic Escherichia coli O157: H7 on the use of surgical services in a children's hospital. *Can J Surg* 1997; 40: 28–32.
9. Fenton SJ, Kastenmeier A, Pysher TJ, et al. Acute appendicitis in a patient with hemolytic uremic syndrome: an unusual clinical scenario. *Pediatr Surg Int* 2008; 24: 439–441.

10. Cimolai N, Anderson JD, Bhanji NM, et al. Escherichia coli O157: H7 infections associated with perforated appendicitis and chronic diarrhoea. *Eur J Pediatr* 1990; 149: 259–260.
11. Emil S, Rockstad R and Vannix D. Hemolytic uremic syndrome in a child with burn injuries. *J Burn Care Rehabil* 1998; 19: 135–137.
12. Anacleto FE, Cifra CL and Elises JS. Postpartum hemolytic uremic syndrome in a 17-year-old Filipina primigravid. *Pediatr Nephrol* 2003; 18: 1283–1285.
13. Bruyand M, Mariani-Kurkdjian P, Gouali M, et al. Hemolytic uremic syndrome due to Shiga toxin-producing Escherichia coli infection. *Med Mal Infect* 2018; 48: 167–174.
14. Kakoullis L, Papachristodoulou E, Chra P, et al. Shiga toxin-induced haemolytic uraemic syndrome and the role of antibiotics: a global overview. *J Infect* 2019; 79: 75–94.
15. McGannon CM, Fuller CA and Weiss AA. Different classes of antibiotics differentially influence shiga toxin production. *Antimicrob Agents Chemother* 2010; 54: 3790–3798.
16. Xiaoli L, Figler HM, Banerjee KG, et al. Non-pathogenic escherichia coli enhance Stx2a production of E. coli O157:H7 through both bamA-dependent and independent mechanisms. *Front Microbiol* 2018; 9: 1325.
17. Bonanno L, Delubac B, Michel V, et al. Influence of stress factors related to cheesemaking process and to STEC detection procedure on the induction of Stx phages from STEC O26: H11. *Front Microbiol* 2017; 8: 296.
18. Ohara T, Kojio S, Taneike I, et al. Effects of azithromycin on shiga toxin production by Escherichia coli and subsequent host inflammatory response. *Antimicrob Agents Chemother* 2002; 46: 3478–3483.
19. Amran MY, Fujii J, Kolling GL, et al. Proposal for effective treatment of Shiga toxin-producing Escherichia coli infection in mice. *Microb Pathog* 2013; 65: 57–62.
20. Nitschke M, Sayk F, Härtel C, et al. Association between azithromycin therapy and duration of bacterial shedding among patients with Shiga toxin-producing enteroaggregative Escherichia coli O104: H4. *JAMA* 2012; 307: 1046–1052.
21. Zhang Q, Donohue-Rolfe A, Krautz-Peterson G, et al. Gnotobiotic piglet infection model for evaluating the safe use of antibiotics against Escherichia coli O157: H7 infection. *J Infect Dis* 2009; 199: 486–493.