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Case report

Shigella sonnei and hemolytic uremic syndrome: A case report and literature review

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ABSTRACT

Hemolytic uremic syndrome (HUS) is a well-described process that is known to cause severe renal dysfunction, thrombocytopenia, and anemia. HUS is typically associated with toxins (shiga-like and shigella toxin) found in strains of *E. coli* and *Shigella* spp [1–3]. We present a case of a 27 year-old man with jaundice, thrombocytopenia, and renal dysfunction who was found to have HUS in the setting of *Shigella sonnei* infection. Outside of developing countries, cases of HUS related to *S. sonnei* are largely unreported.

Introduction

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy characterized by thrombocytopenia, anemia, and renal dysfunction. HUS can have long-term consequences including hypertension, reduced renal function that may be chronic, neurologic sequelae, and death [1,4]. It most commonly occurs in the setting of infection caused by enterohemorrhagic *E. coli* (EHEC) and *Shigella dysenteriae* serotype 1. However, other less common infectious etiologies have also been implicated: bacteria such as *Citrobacter* and *Streptococcus pneumoniae*, viruses such as HIV, EBV, and H1N1, and in the post-kidney transplantation state influenza A, parvovirus and CMV [5,6].

The unifying trait among the most common causes of HUS is the ability to produce and release shiga or shiga-like toxins (Stx). After ingestion of the pathogen, Stx is produced by the microorganism and absorbed by the gut epithelium into the circulation. The toxin is then able to bind to the glycolipid receptor globotiraosylceramide (Gb3), which is expressed in the kidney and brain [1–3,7–9]. After receptor binding, the toxin is internalized, leading to a complex constellation of events including coagulation and inflammation.

Shigella sonnei is the most common type of *Shigella* species in developed countries, including the United States. To date, there is limited documented association of *S. sonnei* and HUS in developed or developing nations. Recognizing HUS caused by atypical infectious organisms is important because HUS is a medical emergency that requires urgent management. It is important *not* to remove HUS from the differential diagnosis just because stool studies do not identify a Shiga toxin or cultures do not grow *E. coli* or *Shigella dysenteriae.*

Case presentation

A previously healthy 27-year old man presented to his primary care provider with 2 days of subjective fever, chills, headache, abdominal pain, vomiting, dark urine (despite adequate hydration), and at least 24 loose "dark brown to black" stools. He was told he had streptococcal pharyngitis and given a prescription for azithromycin. One day later he was hospitalized at an outside facility for worsening symptoms. Laboratory evaluation there showed platelets 4 K/mm^3, hemoglobin 11.4 g/dL, LDH 2070 U/L, haptoglobin 7 mg/dL, creatinine 2.3 mg/dL, and UA positive for blood and protein. Peripheral smear revealed presence of schistocytes. He was given intravenous corticosteroids and ceftriaxone prior to transfer to our facility for further management.

On physical examination temperature was 37 °C, pulse 69/minute, and blood pressure 135/75 mmHg. He had scleral icterus, abdominal tenderness, cutaneous jaundice, and petechiae on his arms and torso. Laboratory evaluation showed sodium 137 mEq/L, potassium hemolyzed, BUN 41 mg/dL, creatinine 2.1 mg/dL, WBC

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6.2 K/mm^3, hemoglobin 11.4 g/dL, platelets 3 K/mm^3, total bilirubin 5.4 mg/dL (direct 0.3), fibrinogen 358 mg/dL, reticulocyte count 1.8%, and LDH 2028 U/L. Urinalysis was significant for 2+ blood. Abdomen/Pelvis CT revealed heterogeneous enhancement of the right renal cortex without evidence of obstruction, nonspecific colonic hyper-attenuation without evidence of acute bowel inflammation, and a small volume of free fluid in the pelvis. Other labs ordered on hospital day 1 included ADAMTS13 and stool studies to evaluate for presence of *E. coli*/Shiga toxin; however, stool studies were unable to be collected until hospital day 3 as diarrhea had strangely abated, and ADAMTS13 had to be sent out to another laboratory.

The working diagnosis on admission was thrombotic thrombocytopenic purpura (TTP), as his diarrhea had resolved at the time of transfer and no stool samples had been collected during his severe diarrheal illness. Due to the emergent nature of his condition, he was treated with plasma exchange and corticosteroids, but antimicrobials were not continued during his hospitalization at our facility. He received a total of three plasma exchange treatments for possible TTP while awaiting ADAMTS13 results. His platelet count increased daily (counts from hospital day 1 were 5, 20, 86, and 176 K/mm^3).

A stool sample was collected and cultured on hospital day 3, and the Shiga toxin EIA was negative. The ADAMTS13, which was sent to Mayo Clinic Laboratories in Rochester, MN, resulted on hospital day 4, with ADAMTS13 activity of 81% (>70% normal). Plasma exchange and intravenous corticosteroids were discontinued given the now more likely diagnosis of HUS. On hospital day 5, stool cultures resulted positive for a *Shigella sonnei* isolate. Platelet count, renal dysfunction, and hemolysis continued to resolve even after discontinuing plasma exchange and corticosteroids, which is consistent with HUS.

Unfortunately, this patient had no insurance, and because he was self-pay, he was insistent that he be discharged as soon as possible. At the time of discharge on hospital day 5, his platelet count was 214 K/mm^3, creatinine was 1.2 mg/dL and LDH was 196 U/L. He was seen by his primary care provider within two weeks of discharge, and 3 months after that, symptoms had not recurred when a member of the team contacted him. The patient declined recommended follow-up laboratory investigation to ensure continued resolution of thrombocytopenia and renal dysfunction.

Discussion

For over 20 years, *Shigella dysenteriae* type 1 and EHEC have been known to cause hemorrhagic colitis via production of Shiga toxin (Stx) or Shiga-like toxins (Stx-1 and Stx-2), respectively [1–3,7]. A more serious complication related to infection with these microbes is hemolytic uremic syndrome (HUS). We present a case of HUS in the setting of *Shigella sonnei* isolated from stool culture, which prompts a discussion on the mechanisms of how Shiga toxins cause HUS and how bacteria that do not typically cause HUS can obtain genes for these toxins. First, it is important to discuss the possibility that EHEC infection was present in this patient but missed in laboratory evaluation. A stool sample was not collected during the early phase of his diarrheal illness, and studies have shown that samples cultured 6–7 days after onset of diarrhea have sensitivity for detecting EHEC as low as 33% [10]. Furthermore, Shiga toxin EIA is 33–76% sensitive, and can be falsely negative in EHEC infections if tested later in the course of illness when lysogenic phages are less numerous; in contrast, PCR is known to be more sensitive, reaching over 90% in some studies [11,12]. Rectal swab earlier in the course, testing the *S. sonnei* isolate for stx genes, and further evaluating for EHEC serologies or PCR may have helped better elucidate *S. sonnei*'s true role in this patient's case of HUS.

Shiga toxins are type 2 ribosome-inactivating proteins, or RIPs, that consist of an A subunit surrounded by 5 identical B subunits, which are responsible for the toxin's ability to enter target cells [8,9]. *Shigella dysenteriae* produces its toxin via activation of the chromosomally located stx gene; but the EHEC Stx-1 and Stx-2 are produced via lysogenic incorporation of genes carried into the bacterium by lambdoid bacteriophages, followed by the lytic cycle that allows for toxin release [8,9,13,14].

Infection of the GI tract with these bacteria typically causes a watery diarrhea; however, development of hemorrhagic colitis indicates toxin production and risk for extra-intestinal disease, including HUS. Once the Shiga toxins gain access to the circulation, they affect target organs by binding to Gb3 receptors located in the kidney and brain. This allows Shiga toxin entrance into renal tissues, followed by inflammation, lysis, and destruction of those cells. Destruction of glomerular cells can cause hematuria, and severe cases of HUS may require dialysis. Gb3 is also expressed on platelets, causing activation, aggregation, and severe thrombocytopenia, and eventually causing microvascular thrombosis [8].

The process described above reviews the well-described pathophysiologic mechanism of toxins produced by EHEC and *Shigella dysenteriae*. However, most of the clinical and scientific data available focus only on toxin production by these two bacterial species. The case we report above appears to be a case of HUS related to intestinal *Shigella sonnei* infection, although EHEC certainly may also have been present. Upon more extensive review of the literature, there is convincing evidence that *Shigella sonnei* has been shown to acquire genes that enable it to produce Stx-1 and Stx-2.

As mentioned above, genes for Stx are known to be carried in lambdoid prophages, or "Stx-converting bacteriophages," which can insert DNA into bacterial host chromosomes via transposition or recombination [13]. *E. coli* and *Shigella* spp. are close genetic relatives, enabling *Shigella* spp to obtain toxin genes from *E. coli*. This indicates that a previously non-toxigenic *Shigella sonnei* could obtain virulence genes if invaded by a phage carrying the toxin genes, and in fact, several researchers have isolated *Shigella sonnei* that produce either Stx-1 and Stx-2a [13,15–17]. The question then arises, how does a non-toxin producing *Shigella sonnei* bacterium come into contact with a bacteriophage carrying Stx genes typically found in *E. coli*? One study looking at two separate urban wastewater treatment plants found that there were Stx gene-carrying phages in samples of raw sewage as small as 10 mL, with an estimated 1–10 free phages/mL of sewage [18]. Another study sampled feces from 100 healthy individuals and found that 62% of samples carried Stx gene-carrying phages, which were able to infect and propagate in cultures of Stx-negative *E. coli* C600 and O157:H7, as well as *Shigella sonnei* [19]. These free Stx-2 phages survive longer in water environments than their bacterial hosts and remain infective, allowing them to transfer stx genes when they do come into contact with a host [20]. Other possibilities include conversion of typically non-HUS producing bacterium (such as *Shigella sonnei*) into HUS-producing strains inside the intestinal tract by ingestion of free Stx-carrying bacteriophages from contaminated food or water or by co-infection with an Stx-toxin producing *E. coli* or *Shigella dysenteriae* that lyses and releases bacteriophages in the intestine, the latter of which is certainly a possibility in our patient [8,19].

Common practice dictates that one should treat *Shigella* diarrheal illnesses, typically with ceftriaxone or ciprofloxacin; however, special attention to monitoring for HUS should be given when using ciprofloxacin or trimethoprim-sulfamethoxazole. These and other antimicrobials are known to trigger increased production of Shiga toxin when the SOS response inactivates the phage cI repressor protein, leading to activation of stx genes and transition from lysogenic to lytic phase [8,9,13,21,22]. One study

reported that HUS developed in 5 out of 9 children (56%) given antibiotics for *E. coli* O157:H7 diarrhea compared to 5 out of 62 (8%, $P < 0.001$) who were not given antibiotics [21]. In contrast, meropenem and azithromycin have been shown to reduce phage induction and Stx2 production, and may therefore be safe treatment options for EHEC infections [23,24]. Our patient did receive azithromycin early in his course of illness and it may have contributed to earlier resolution of his diarrhea, but does not seem to have prevented development of HUS.

Conclusion

Although the organisms that are well known to be associated with HUS are *Shigella dysenteriae* serotype 1 and *E. coli* O157:H7, our case and the discussion presented above indicates that clinicians must still be astute in monitoring for HUS when treating illness due to other *Shigella* organisms, such as *S. sonnei*. Use of certain antimicrobials can put patients with EHEC at risk of increased Shiga toxin production, but azithromycin is likely a safe option for those with severe infections. Of note, increased toxin production secondary to antimicrobial use is not applicable to *Shigella dysenteriae*, whose gene is chromosomally located and therefore not dependent on the SOS response and phage lytic phase. We propose checking platelet count and creatinine 1 week after onset of diarrheal illness to monitor for signs of HUS. There is no reported evidence to support this; however, one study from Bangladesh reported 30 children with *S. sonnei* who were admitted to the hospital at a median of 5 days into diarrheal illness, 2 of whom were also diagnosed with HUS [25].

Conflicts of interest

None.

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