

CLINICAL VIGNETTE

Shiga Toxin Mediated Hemolytic Uremic Syndrome in a Patient with Systemic Lupus Erythematosus

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A 39-year-old female with severe polyarthritis associated with systemic lupus erythematosus (SLE) presented to the hospital with one day of abdominal pain, nausea, vomiting, and diarrhea. She reported episodes of bloody diarrhea and non-bloody, non-bilious vomiting.

Current immunosuppressive medications included upacatinib (Rinvoq) (Jak kinase inhibitor DMARD), hydroxychloroquine (Plaquenil), and methylprednisolone.

In the emergency room, she was afebrile with normal vital signs and normal oxygen saturation. Her exam was notable for diffuse abdominal tenderness, without peritoneal signs.

Initial labs included normal BUN and creatinine (16/0.82), elevated WBC of 17.2, mild transaminase elevation ALT 199, AST 91, and normal bilirubin and PT/PTT.

CT scan of the abdomen was significant for severe diffuse colonic wall thickening, right greater than left, suggestive of colitis, including possible pseudomembranous colitis. Stool bacterial PCR was positive for *Escherichia coli* serogroup O157.

Shiga Toxin 2 was positive on Rapid Membrane Enzyme Immunoassay. Shiga Toxin 1 was not detected.

She was treated with supportive care, bowel rest, IVF, and electrolyte repletion. By hospital day 3, she had minimal to no improvement. Labs noted worsening acute kidney injury, leukocytosis, anemia, and thrombocytopenia. Hemoglobin declined from 13 to 8gm/dL. She also developed indirect hyperbilirubinemia (4.0/1.9), with low haptoglobin (16mg /dL) and elevated LDH (2, 140 units/L). D dimer 37, 120ng/mL, fibrinogen 459, ADAMTS 13 activity low (42%). DAT coombs test negative. Manual differential revealed shistocytes.

Pathogenic *E. Coli* are among the most frequent causes of diarrhea.¹ *Escherichia coli* containing genes encoding Shiga Toxin 1 and 2 are important human pathogens known as Shiga toxin producing *E. Coli* (STEC).¹ *E. coli* O157:H7, can cause severe disease, with painful bloody diarrhea, and the hemolytic uremic syndrome (HUS).¹ STEC HUS is a life-threatening disease characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute renal injury. This affects 6-9% of patients with STEC infections.²

Shiga toxic producing *E. coli* (STEC) that contain the gene encoding Shiga toxin 2 are often associated with bloody diarrhea and can cause HUS. The greatest burden of severe STEC infection and HUS occurs in children < 5 years of age, followed by adults > 60 years old.² The most common route of transmission is foodborne but can also occur through contact with colonized animals, infected individuals and contaminated water. STEC is primarily prevented by avoiding exposure, by cooking meats adequately, avoiding unpasteurized dairy, and using proper hand hygiene.³

After consuming STEC contaminated food or water, STEC colonizes the colonic epithelium. Shiga toxins, which are the main virulence factors of STEC, are released and further damage the vascular network of the intestinal mucosa causing hemorrhagic colitis.³ Once Shiga toxin enters the systemic circulation, it can bind with granulocytes and platelets and be transported to the kidney and other target organs.³

STEC-HUS cause shiga toxin-mediated injury to vascular endothelial cells in the kidney, brain, and other organs. These potent cytotoxins are released by bacteria in the gut, enter the bloodstream and cause endothelial injury by binding to the globotriaosylceramide (Gb3) receptor on the plasma membrane of endothelial cells, podocytes, and proximal tubular cells.^{2,4,5} Shiga toxin also activates the alternative pathway of the complement system by binding to factor H proteins, known as complement control proteins, and reducing their cell surface activity.⁶

Clinically, the diagnosis of STEC-HUS relies on a complete careful history with corresponding clinical symptoms, and laboratory testing. Presence of thrombotic microangiopathy (TMA), non-immune hemolytic anemia, microangiopathic hemolytic anemia (MAHA), (hematocrit < 30% with shistocytes in peripheral blood smear and a negative Coomb's test), thrombocytopenia (platelet count < 150, 000mm³), AKI, with or without hypocomplementemia.³ If STEC-HUS is suspected, fecal and serological testing for STEC is required.⁷ History should include exposure to risk factors for STEC such as consumption of unpasteurized dairy products, raw beef or cattle products, contact with patients experiencing diarrhea, or goats and sheep.³

Bacteriological investigation is the gold standard for the diagnosis of STEC infections. Other intestinal pathogens such as Salmonella, Shigella, Campylobacter, Yersinia, Clostridiodes difficile should be excluded by fecal culture. Fecal culture needs to be combined with polymerase chain reaction (PCR) to detect the Stx-encoding gene which improves the detection rate, and further distinguishes non-0157 from 0157 infections.^{8,9}

Serologic testing to detect the STEC LPS antibody is also useful especially if bacterial isolation has failed.³ Increasing evidence supports the role of complement activation in the development of STEC HUS,¹⁰ and C3 and C4 should be measured.³

After thrombocytopenia and microangiopathic hemolytic anemia (MAHA) have been confirmed, other primary thrombotic microangiopathies should be considered.

TTP is caused by severe ADAMTS-13 deficiency (activity < 10%).¹¹ ADAMTS13 is the protease that cleaves large von Willebrand factor multimers in the vasculature, and its deficiency promotes formation of platelet microthrombi. Deficiency of ADAMTS13 can be hereditary or immune mediated. The PLASMIC score is an algorithm developed to estimate the probability of ADAMTS13 activity <10 percent (and diagnosis of TTP) in a patient with MAHA and thrombocytopenia to initiate therapeutic plasma exchange while awaiting ADAMTS13 activity. TTP typically results in minimal abnormalities of kidney function, has more severe thrombocytopenia and more systemic manifestations of organ injury than the other primary TMA syndromes.¹¹

The mean incubation period for STEC is approximately 3.5 to 8 days.¹² Typical clinical presentation includes watery diarrhea for 3-5 days that progresses to bloody diarrhea and severe abdominal pain, with nausea and vomiting. Thrombocytopenia and AKI develop 2-14 days after onset of diarrhea.¹³ About 20% of patients with STEC-HUS have extrarenal manifestations including neurological symptoms, pancreatitis, intestinal necrosis or perforation, finger or toe gangrene, ulcerative necrotizing skin lesions, myocardial infarction, and ischemic cardiomyopathy.¹³

Treatment of STEC-HUS relies heavily on supportive care, which includes fluid resuscitation, the correction of electrolyte abnormalities, and control of hypertension.¹⁴ Blood and platelet transfusions and renal replacement therapy (RRT) are often required.¹⁵ Other treatments include plasma exchange and eculizumab,¹⁶ a monoclonal antibody directed against complement protein C5 to prevent complement activation. With supportive treatment, around 30% of patients develop long term sequelae, including renal and neurological complications.¹⁷ Notably, antibiotics are *not* recommended in Shiga toxin producing E. Coli infections because of the association with hemolytic uremic syndrome.¹⁸ Antibiotic therapy is reasonable in patients with diarrhea associated with other severe pathogenic E. coli infections (such as E. coli 0157:H7) with bloody stools, fever, > 6 stools per day, volume depletion warranting

hospitalization, or in immunocompromised patients. Azithromycin or a fluoroquinolone are appropriate antibiotics.

In summary, this 39-year-old female with immunosuppression and RA/SLE overlap presented with abdominal pain and diarrhea. She was found to have Shiga toxin positive colitis leading to HUS. Clinical and laboratory findings concerning for TMA included MAHA, + Shiga toxin, and clinically consistent Shiga-toxin mediated Hemolytic uremic syndrome (HUS). The patient also developed fever and encephalopathy concerning for Thrombotic thrombocytopenic purpura (TTP). Her course was complicated by seizures and multiorgan failure requiring transfer to ICU, mechanical ventilation, renal replacement therapy, vasopressors, and TPN. Multidisciplinary care was provided including consultation by hematology, nephrology, pulmonary critical care, rheumatology, gastroenterology and nutrition. She was started on plasma exchange and eculizumab. She was transferred from community hospital to a tertiary care ICU. Our case highlights the need for clinicians to have clinical suspicion for HUS in the setting of diarrheal illness in order to promptly diagnose and treat this life threatening condition. Fortunately, after a 3 month hospital stay, our patient improved. She was able to tolerate oral diet, breathing on room air, improved renal function not requiring hemodialysis, stable hemoglobin and hematocrit, and was discharged home with close follow up.

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