CLINICAL VIGNETTE

Shiga Toxin-Induced Hemolytic Uremic Syndrome in a 17-Year-Old Woman

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Case Report

A 17-year-old woman presented to the emergency department with one day of fever, intermittent cramping abdominal pain and bloody diarrhea. One-month prior she completed a five-day course of antibiotics following a tooth extraction. Five days prior she was exposed to animals at a petting zoo. She was a vegan and denied recent changes in diet. She had no personal or family history of inflammatory bowel disease, cancer or autoimmune disease. Her previous medical history was significant for migraines controlled with rizatriptan. On physical exam, her temperature was 100.1°F, heart rate 117, blood pressure 123/74. Her abdomen was soft and tender to palpation greatest at the right upper quadrant without rebound or guarding. Rectal examination revealed guaiac positive brown stool. Laboratory data were notable for a white blood cell count of 13.6 cell/mm^3, hemoglobin of 12.6 g/dL, platelets of 226 cells/mm^3 and potassium of 3.5 mmol/L. Her creatinine was 0.7 mg/dL and liver enzymes were normal. C-reactive protein and erythrocyte sedimentation rate were 11.5 mg/dL and 20 mm/hr respectively. Stool culture was positive for Escherichia coli 0157:H7 and the abdominal computed tomography (CT) scan showed pancolitis.

She received ciprofloxacin and metronidazole in the emergency department, which was discontinued on the second hospital day. She continued to have loose bloody bowel movements that improved over 5 days. Over the course of her hospitalization her creatinine rose to 6.4 mg/dL, the hemoglobin dropped to 5.3 g/dL and the platelet count dropped to 70 cells/mm^3. A lactate dehydrogenase level was elevated at 1014 IU/L. Blood smear initially revealed rare schistocytes, quantified as 1/HPF, and this increased to 2-3/HPF over the subsequent hospital days. ADAMTS13, prothrombin time, partial thromboplastin time, antinuclear antibody, and screening for human immunodeficiency virus were all normal or negative. The patient experienced headaches consistent with her history of migraines; however, she maintained a normal sensorium and the neurological examination remained normal. She continued to have adequate urine output despite her renal failure. Based on history, physical exam and laboratory findings, she was diagnosed with shiga-toxin induced hemolytic uremic syndrome. In consultation with Hematology the patient received 900 mg of eculizumab and 2 units of packed red blood cells. Her creatinine improved to 1.33 mg/dL at the time of discharge. She received eculizumab 900 mg once weekly for one month and was continued on folic acid 1 mg daily. After three months, her renal function and complete blood count normalized completely to her baseline.

Background

Hemolytic uremic syndrome (HUS) is a disease of microangiopathic hemolytic anemia, thrombocytopenia and renal failure. HUS is most likely to occur in young children and the elderly. It develops either as a result of complement dysregulation, or from secondary causes, such as infection, including Shiga-toxin-producing E. coli, Streptococcus pneumoniae, human immuno-deficiency viral (HIV) infection, or from drug toxicity[1]. It rarely occurs in pregnancy or in autoimmune disorders. Neurologic complications including seizures, coma and hemiparesis develop in a quarter of patients. Half of patients require dialysis and three quarters receive red cell transfusions. The mortality rate is 3-5% and approximately 5% of survivors have end-stage renal disease or permanent neurologic injury[2-3].

E. coli O157:H7 is the most important serotype of enterohemorrhagic E. coli in terms of public health and is responsible for most cases of HUS[4]. It typically presents with severe abdominal cramping and non-bloody diarrhea, which may become grossly bloody (hemorrhagic colitis) by the second or third day of illness. Unlike most bacterial enteric diseases, E. coli O157:H7 is usually characterized by a low-grade fever or absence of fever that may lead clinicians to suspect non-infectious diagnoses at the time of presentation. It is transmitted to humans primarily through consumption of contaminated foods, such as undercooked ground meat, raw milk

and contaminated raw vegetables and sprouts[5]. Treatment with antibiotics or antimotility agents is thought to increase the risk of development of HUS. The mechanisms by which E. coli O157:H7 cause diarrhea and HUS are not completely understood. The organism is known to produce one or more verotoxins, also known as Shiga-like toxins because of their similarity to the toxin produced by Shigella dysenteriae. Recent evidence suggests the toxin activates complement, which leads to microvascular injury, microangiopathic hemolysis and renal and central nervous system (CNS) perfusion abnormalities.

Shiga toxin-mediated HUS is historically defined as "typical HUS" and is responsible for 90% of all cases of HUS. Atypical HUS is a rare disease that comprises a heterogeneous group of patients in whom infection with Shiga-toxin producing bacteria could be excluded as the cause of disease. Atypical HUS commonly develops due to dysregulation of the alternative pathway of complement secondary to a myriad of genetic mutations[6-7].

Management

Treatment of HUS is primarily supportive, including red cell transfusion for anemia when clinically indicated, platelet transfusion for patients with significant clinical bleeding, appropriate fluid and electrolyte management, stopping nephrotoxic agents, and provision of adequate nutrition. Initiation of dialysis therapy is used according to clinical guidelines (i.e., symptomatic uremia, azotemia, severe fluid overload and/or electrolyte abnormality). Two recent reports described patients with severe Shiga-toxin mediated HUS and CNS toxicity that were treated with eculizumab with good recovery. Eculizumab is a monoclonal antibody to complement factor C5 that blocks complement activation and has been used in the treatment of patients with complement-mediated HUS, although its benefit has not been clearly demonstrated[8-9].

Conclusion

In summary, hemolytic uremic syndrome (HUS) is a disease of non-immune microangiopathic hemolytic anemia, thrombocytopenia and renal failure, with neurologic complications developing in one quarter of patients. Shiga toxin-producing E. coli is responsible for the majority of cases of HUS in children, and patients often present with low-grade fever, cramping abdominal pain, and bloody diarrhea. Differentiating the disease from other conditions is important for proper management. Initial management of patients with HUS is supportive. The decision to use eculizumab in the treatment of patients with complement-mediated HUS is made on a case-by-case basis.

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