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Clinical Case Study

A 4-Year-Old Girl with Gastroenteritis, Anemia, Thrombocytopenia, and Hematuria

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CASE DESCRIPTION

A previously healthy 4-year-old girl presented with a 2-day history of severe nausea, vomiting, and diarrhea. Her symptoms began with diffuse abdominal pain followed by alternating episodes of vomiting and nonbloody diarrhea. There were no reports of sick contacts, recent travel, camping, or unusual food or water consumption. On the first day of symptoms, her primary care physician diagnosed viral gastroenteritis and stool cultures were sent to an outside laboratory. The following day, her vomiting increased in frequency and the diarrhea became streaked with blood and mucus. The patient was taken to a regional hospital where a complete blood count revealed a white blood cell count of 22 500/mL (reference interval, 5.5–15.5 × 1000/mL) with 89% neutrophils and 7% bands. A urinalysis revealed positive ketones of 150 mg/dL (reference value, negative) and a specific gravity of 1.030 (reference interval, 1.005–1.030). She was then transferred to our hospital for management of neutrophilia and dehydration. On admission, her temperature was 38.7 °C, but other vital signs and physical exam results were unremarkable. She was treated with intravenous fluids. Stool cultures for bacteria, shiga toxin, ova, and parasites were obtained. Urinalysis showed positive protein of 300 mg/dL protein (reference value, negative) and 4 red blood cells per high-power field (reference value, negative). On day 2 of admission, the patient passed cranberry-colored urine. Repeat laboratory test results at this time revealed creatinine of 1.10 mg/dL (97.2 μmol/L) (reference interval, 0.03–0.7 mg/dL), a blood urea nitrogen (BUN)[4] of 26 mg/dL (9.3 mmol/L) (reference interval, 6–20 mg/dL), a hematocrit of 30.7% (reference interval, 34.0%–40.0%), and a platelet count of 28 000/mL (reference interval, 150–450 × 1000/mL). Her blood smear is shown in Fig. 1. She continued to demonstrate anemia and thrombocytopenia throughout her hospital admission. Her stool cultures (and blood cultures) sent on admission were negative for pathogens.

QUESTIONS TO CONSIDER

1. What diagnosis is most likely in light of the clinical presentation?
2. What laboratory tests or radiologic imaging is/are required to make the appropriate diagnosis?
3. What organisms are typically implicated in this disease?
4. What is the expected clinical course of this disease?

DISCUSSION

Hemolytic uremic syndrome (HUS) is defined by a triad of microangiopathic hemolytic anemia (characterized by schistocytes and helmet cells, as shown in Fig. 1), thrombocytopenia, and renal dysfunction. It is a leading cause of acquired renal failure in children in the US. In almost all diagnosed HUS cases there is a preceding diarrheal illness, which defines typical HUS. The most common pathogens causing HUS are *Escherichia coli* (specifically toxin-producing O157:H7, along with other *E. coli* strains), followed by *Shigella*, and finally, a variety of other less common bacterial causes. If the disease is not preceded by a diarrheal prodrome, then it is considered atypical HUS.

HUS presents most commonly in young school-aged children. In typical HUS, the onset of complications occurs 3–7 days (but can be up to 14 days) after the onset of the symptoms of gastroenteritis. These intestinal symptoms may be severe enough to cause hospitalization secondary to dehydration or self-limiting with only mild symptoms. Oliguria due to renal damage can be missed early in the illness because it may be thought to be associated with dehydration from the ongoing diarrheal losses or poor oral intake.

Microangiopathic hemolytic anemia is one of the key features that define HUS. It is characterized by a negative Coombs test despite ongoing hemolysis, and hemoglobin values are generally <8 g/dL. The periph-

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[4] Nonstandard abbreviations: BUN, blood urea nitrogen; HUS, hemolytic uremic syndrome; CNS, central nervous system.

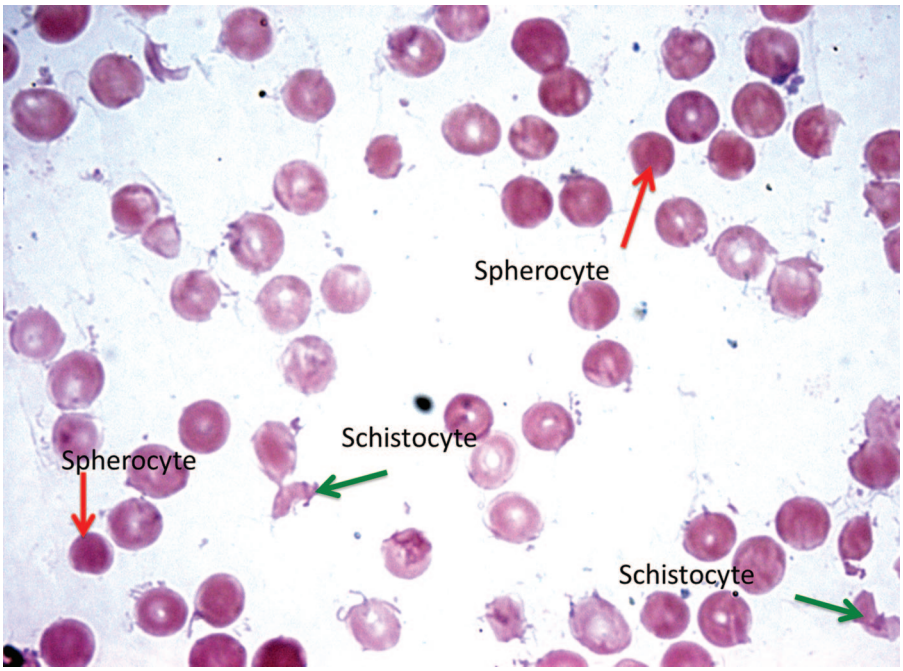

Fig. 1. Patient's blood smear.
Spherocytes and schistocytes are indicated by arrows.

eral blood smear can show up to 10% schistocytes, along with helmet cells, which are produced due to damage of the endothelial layer of small vessels, resulting in fibrin deposition and platelet aggregation. As a result, as the red blood cells travel through these vessels, they are damaged and fragmented, resulting in intravascular hemolysis. An increased lactate dehydrogenase concentration is the most sensitive index of ongoing hemolysis. Additional findings include increased indirect bilirubin, reticulocytosis, and a sharp decrease in haptoglobin.

Thrombocytopenia is another component of the triad. Platelet counts are below 140×10^3/mL but usually stay above 40×10^3/mL and do not typically lead to clinically significant bleeding. Results of coagulation studies typically remain within reference intervals.

Diagnosis is made by evidence of microangiopathic hemolytic anemia (anemia, thrombocytopenia, and schistocytes/helmet cells seen on blood smear) with some evidence of renal insufficiency. Although the hemolytic anemia may be severe, it does not typically correlate with the severity of renal disease. In typical HUS, a stool culture may be obtained to isolate the most common causes of HUS. *E. coli* O157:H7 should be cultured using MacConkey agar because this particular strain does not ferment sorbitol. Leukocytosis is usually present, but its absence does not rule out the disease. Urinalysis will usually show microscopic hematuria and a small amount of proteinuria. Ketones may also be seen secondary to the catabolic state from general illness. Renal involvement ranges from mild with only slight increases in BUN and creatinine to acute severe anuric kidney failure requiring dialysis.

Complications of HUS include severe anemia from microangiopathic hemolytic anemia, volume overload and hypertension from anuria or oliguria, hyperkalemia from hemolysis of erythrocytes in combination with renal insufficiency, and various other electrolyte abnormalities. Heart failure and arrhythmias can occur secondary to severe anemia and volume overload or depletion. Patients may also exhibit glucose intolerance and transient diabetes mellitus during the acute phase of HUS due to inappropriately low serum insulin. Many patients will present with some form of central nervous system (CNS) disease, including irritability, lethargy, and other nonspecific mild encephalopathic symptoms. Severe CNS involvement is rare, affecting only 15% to 20% of children with documented HUS. CNS symptoms result from focal ischemia to the nervous system from microvascular involvement, which parallels the disease of the kidney. Up to 50% of patients with typical HUS will develop

POINTS TO REMEMBER

- HUS leads to microangiopathic hemolytic anemia, thrombocytopenia, and nephropathy.
- HUS is frequently associated with a prodromal diarrheal illness.
- *Escherichia coli* is the most common bacterial etiology of typical HUS.
- Laboratory findings may include abnormal urinalysis findings (proteinuria, hematuria, or casts), schistocytes on blood smear, anemia, thrombocytopenia, increased BUN and creatinine, hyperkalemia, and coagulation study results within reference intervals.
- HUS can affect many organ systems, including renal, nervous, gastrointestinal, hematologic, endocrine, skin, and cardiovascular systems.

oliguric renal failure and require dialysis during the acute phase, but the prognosis for recovery of renal function is generally favorable.

Treatment is usually supportive, with considerable care being taken to monitor for complications and to monitor fluid status. Packed red blood cell transfusions may be needed for patients with severe symptomatic anemia (e.g., hematocrit <18%). The practitioner should avoid platelet transfusions when possible because the platelets will be consumed by the ongoing hemolysis and can theoretically worsen the clinical course. Anticoagulation and fibrinolytic and antiplatelet therapy are contraindicated owing to the increased risk of serious hemorrhage. Antibiotic therapy can exacerbate the disease process by increasing toxin release and is therefore not recommended. If required, the patient may need to undergo dialysis. Dialysis is usually reserved for patients with BUN >80 mg/dL (>28.6 mmol/L). Most patients with typical HUS have no long-term sequelae.

On review of our patient's cultures sent from the primary pediatrician's office before her admission at our facility, we found that the patient's original stool culture contained *E. coli* O157:H7 that was positive for shiga toxin, thus confirming our diagnosis of typical HUS.

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Commentary

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Microangiopathic hemolytic anemia, acute renal dysfunction, and thrombocytopenia are the triad of symptoms consistent with HUS. HUS can be a consequence of infection with shiga toxin–producing *Escherichia coli* (STEC),[2] also known as enterohemorrhagic *E. coli*.

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[2] Nonstandard abbreviations: STEC, shiga toxin–producing *Escherichia coli*; SMAC, MacConkey agar with sorbitol.