CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 19-2018: A 15-Year-Old Girl with Acute Kidney Injury

Ann Y. Kao, M.D., M.P.H., Pallavi Sagar, M.D., Jean E. Klig, M.D.,
Amita Sharma, M.D., and Kristen J. Tomaszewski, M.D.

PRESENTATION OF CASE

Dr. Helen I. Healy (Pediatrics): A 15-year-old girl was admitted to this hospital during the summer because of acute kidney injury.

The patient had been well until 8 days before admission, when painful cramping in the lower abdomen and bloody diarrhea developed. Bowel movements occurred approximately every hour, and the patient was unable to sleep. She took ibuprofen but had no relief of the abdominal pain.

On the third day of illness, two episodes of nonbloody, nonbilious emesis occurred. The following day, the patient was seen by her primary care pediatrician. She reported that she felt fatigued and that the diarrhea, abdominal cramping, and vomiting had persisted; she had not had a fever. The results of a physical examination were normal. Stool samples were obtained for cultures for salmonella, shigella, campylobacter, aeromonas, plesiomonas, and *Escherichia coli* O157:H7, and antigen-detection tests were performed for rotavirus, giardia, and *Clostridium difficile* toxin. The patient was advised to stop taking ibuprofen, to take loperamide and acetaminophen as needed, and to drink an electrolyte-containing oral rehydration solution. During the next 3 days, the diarrhea resolved, but the patient continued to vomit several times each day and the abdominal cramping became localized to the epigastrium. The stool cultures and antigen-detection tests were negative. Her mother called the pediatrician's office on the seventh day of illness, and ondansetron was prescribed.

The following morning, the patient returned to the pediatrician's office because of persistent painful cramping in the epigastrium. On examination, she appeared mildly ill and slightly pale. The temperature was 36.5°C, and the pulse 98 beats per minute. The abdomen was soft, with normal bowel sounds and mild, diffuse tenderness and with no distention, masses, or guarding. The remainder of the examination was normal. Ranitidine and a probiotic were recommended. Two hours after this appointment, the patient's mother called the office to report that the patient had vomited again; she was advised to take the patient to the emergency department at a local hospital for further evaluation and treatment.

From the Departments of Pediatrics (A.Y.K., A.S.), Medicine (A.Y.K.), Radiology (P.S.), Emergency Medicine (J.E.K.), and Pathology (K.J.T.), Massachusetts General Hospital, and the Departments of Pediatrics (A.Y.K., A.S.), Medicine (A.Y.K.), Radiology (P.S.), Emergency Medicine (J.E.K.), and Pathology (K.J.T.), Harvard Medical School — both in Boston.

N Engl J Med 2018;378:2421-9.
DOI: 10.1056/NEJMcpc1802827

Table 1. Laboratory Data.*

Variable	Reference Range, Other Hospital	On Presentation, Other Hospital	Reference Range, This Hospital†	On Presentation, This Hospital
Hemoglobin (g/dl)	12.0–16.0	12.9	12.0–16.0	11.1
Hematocrit (%)	36.0–46.0	36.4	36.0–46.0	30.9
White-cell count (per mm^3)	4500–11,000	9340	4500–13,500	9310
Differential count (%)				
Neutrophils	54.0–62.0	75.6	40–59	66.1
Bands	0.0–7.0	0.9		
Metamyelocytes	0.0	0.9		
Immature granulocytes			0.0–0.3	3.4
Lymphocytes	25.0–50.0	10.4	33–48	16.1
Monocytes	4.7–12.0	7.8	4–11	12.5
Eosinophils	0.0–3.0	3.5	0–8	1.4
Basophils	0.0–1.0	0.9	0–3	0.5
Platelet count (per mm^3)	140,000–440,000	65,000	150,000–450,000	53,000
Red-cell count (per mm^3)	4,500,000–5,300,000	4,970,000	4,100,000–5,100,000	4,230,000
Mean corpuscular volume (fl)	78.0–102.0	73.2	78.0–102.0	73.0
Mean corpuscular hemoglobin (pg)	27.0–31.0	26.0	25.0–35.0	26.2
Mean corpuscular hemoglobin level (g/dl)	32.0–36.0	35.4	31.0–37.0	35.9
Red-cell distribution width (%)	11.5–14.5	12.6	11.5–14.5	12.7
Reticulocyte count (%)			0.5–2.5	1.1
Description of peripheral-blood smear		Anisocytosis, microcytosis, 1+ polychromasia, large platelets		
Haptoglobin (mg/dl)			16–199	<6
Sodium (mmol/liter)	133–145	131	135–145	132
Potassium (mmol/liter)	3.4–4.7	4.0	3.4–5.0	3.9
Chloride (mmol/liter)	98–107	89	98–108	95
Carbon dioxide (mmol/liter)	22–32	18	23–32	17
Anion gap (mmol/liter)	3–17	24	3–17	20
Calcium (mg/dl)	8.9–10.3	8.0	8.5–10.5	7.5
Phosphorus (mg/dl)			3.0–4.5	5.2
Glucose (mg/dl)	65–99	89	70–110	87
Urea nitrogen (mg/dl)	4–18	101	8–25	97
Creatinine (mg/dl)	0.3–1.0	7.53	0.60–1.50	7.71
Protein (g/dl)				
Total	6.1–8.1	6.0	6.0–8.3	4.9
Albumin	3.1–4.8	3.2	3.3–5.0	2.7
Globulin		2.8	1.9–4.1	2.2
Alanine aminotransferase (U/liter)	7–35	249	7–33	186
Aspartate aminotransferase (U/liter)	14–37	161	9–32	120
Alkaline phosphatase (U/liter)	67–372	300	15–350	232
Bilirubin (mg/dl)				
Total	0.0–1.2	1.0	0.0–1.0	0.8
Direct	0.0–0.2	0.3		

Table 1. (Continued.)

Variable	Reference Range, Other Hospital	On Presentation, Other Hospital	Reference Range, This Hospital†	On Presentation, This Hospital
Lipase (U/liter)	13–60	115		
Lactic acid (mmol/liter)			0.5–2.0	0.9
Uric acid (mg/dl)			2.3–6.6	9.0
Lactate dehydrogenase (U/liter)			110–210	2249
Creatine kinase (U/liter)			40–150	108
Parathyroid hormone (pg/ml)			10–60	150
C3 (mg/dl)			81–157	97

* To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110. To convert the values for uric acid to micromoles per liter, multiply by 59.48.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

In the emergency department at the other hospital, the patient reported that the volume of urine output had decreased. On examination, she appeared slightly pale. The temperature was 36.9°C, the pulse 80 beats per minute, the blood pressure 111/69 mm Hg, the respiratory rate 22 breaths per minute, and the oxygen saturation 100% while she was breathing ambient air. The remainder of the examination was unchanged. Laboratory test results are shown in Table 1. Imaging studies of the abdomen were performed.

Dr. Pallavi Sagar: An abdominal radiograph was normal. Abdominal ultrasonography revealed a large amount of layering sludge in the gallbladder, with no thickening of the gallbladder wall (Fig. 1A). Both kidneys were normal in size (length of the right kidney, 11.5 cm; length of the left kidney, 10.6 cm), with mildly echogenic renal parenchyma (Fig. 1B and 1C). The urinary tract was not dilated, and the bladder was partially distended. A moderate amount of ascites was present in the lower abdomen, and a trace amount was present in Morison's pouch (Fig. 1D).

Dr. Healy: Two liters of normal saline were administered intravenously; afterward, the patient did not have any urine output. After consultation with a pediatric nephrologist, the patient was transferred to the emergency department at this hospital.

On arrival, the patient rated her abdominal pain at 3 on a scale of 0 to 10, with 10 indicating the most severe pain. She reported that, during the past week, her weight had decreased by 3 kg and then increased by 1 kg. She had a history of attention deficit–hyperactivity disorder, anxiety, and labial adhesions. During the previous 7 months, she had been seen by her pediatrician on three occasions because of intermittent dysuria; tests for urinary tract infection, chlamydia, and gonorrhea had been negative. Medications included citalopram and methylphenidate; she had an allergy to azithromycin, which had caused a rash. The patient lived with her parents and siblings in New England. Just before the onset of the current illness, she had spent several days in New York City, where she had eaten food purchased from street vendors. She had had no known exposure to sick persons, was not sexually active, and did not smoke cigarettes, drink alcohol, or use illicit drugs. Her maternal grandfather had the antiphospholipid syndrome, her paternal grandmother had hypothyroidism, and her mother had had gestational hypertension; there was no known family history of kidney disease or inflammatory bowel disease.

On examination, the patient appeared tired but otherwise well. The temperature was 36.9°C, the pulse 71 beats per minute, the blood pressure 124/75 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while she was breathing ambient air. The abdomen was soft, with normal bowel sounds and mild tenderness of the upper abdomen and with no distention, masses, or hepatosplenomegaly.

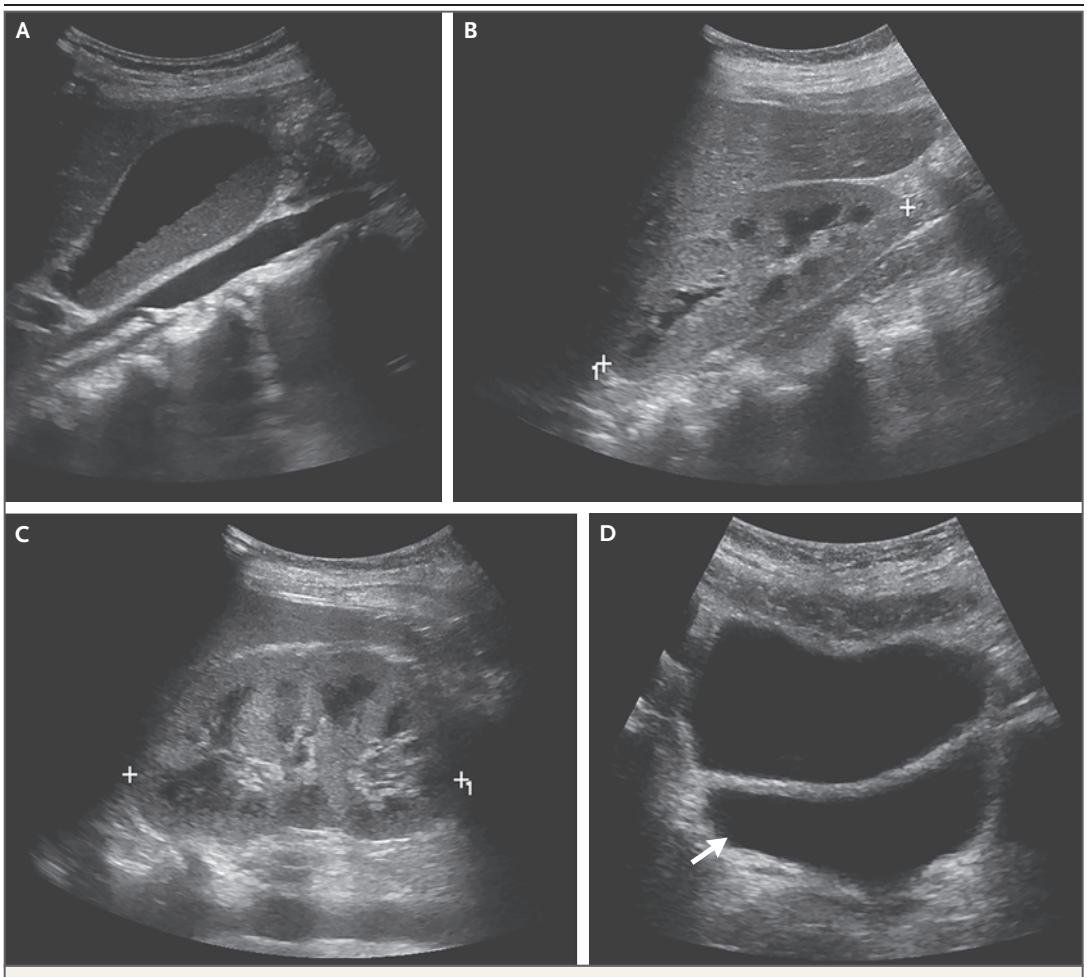

Figure 1. Abdominal Ultrasound Images.

The gallbladder contains a large amount of layering sludge, without wall thickening (Panel A). Both kidneys are normal in size, with mildly echogenic renal parenchyma and without urinary tract dilatation (Panels B and C). The urinary bladder is partially distended, and simple ascites is visible in the pelvis (Panel D, arrow).

There was no pedal or pretibial edema, and the remainder of the examination was unchanged. Laboratory test results are shown in Table 1. An electrocardiogram was normal. After the intravenous administration of 1 liter of normal saline, the patient voided only 2 ml of urine. Urinalysis revealed turbid, amber urine, with 2+ blood, 3+ albumin, 3+ leukocyte esterase, a specific gravity of 1.012, and a pH of 5.0 by dipstick; microscopic examination of the sediment revealed transitional cells, squamous cells, amorphous crystals, mucin, bacteria, and white-cell clumps, as well as 20 to 50 red cells per high-power field and more than 100 white cells per high-power field. A urine pregnancy test was negative. Ultrasonography of the bladder, performed at the bedside, revealed that the bladder was collapsed. Ondansetron was administered intravenously.

The patient was admitted to the hospital, and a diagnosis was made.

DIFFERENTIAL DIAGNOSIS

Dr. Ann Y. Kao: This previously healthy adolescent girl presented with a sudden onset of abdominal cramping and bloody diarrhea. Although the diarrhea resolved on its own, the painful abdominal cramping persisted and emesis developed. By the eighth day of illness, oliguria had developed, and there were findings consistent with acute kidney injury, anemia, and thrombocytopenia on laboratory testing. Through a deeper exploration of each of these key clinical features, I will con-

struct a differential diagnosis and then try to arrive at a unifying diagnosis.

ACUTE KIDNEY INJURY

The severity of the acute kidney injury is the most worrisome aspect of this patient's presentation.[1] In general, causes of acute kidney injury are separated into three categories: prerenal, intrinsic renal, and postrenal or obstructive.[2,3] In this patient, prerenal and intrinsic renal causes warrant closer inspection, whereas obstructive causes can be ruled out, since she did not have evidence of hydroureter, hydronephrosis, or a dilated bladder on ultrasonography.

PRERENAL CAUSES OF ACUTE KIDNEY INJURY

In community-based pediatric practices, cases of acute kidney injury are most commonly caused by prerenal conditions, in which decreased renal perfusion leads to a decreased glomerular filtration rate. In prerenal diseases, renal tubular function remains intact and there is avid resorption of sodium and water in response to the hypoperfusion; as a result, oliguria develops.[3] The most common prerenal cause of acute kidney injury is volume depletion, which can be due to blood loss or excessive loss of water from the gastrointestinal tract, the skin, or the urinary tract. Other prerenal causes include heart failure, distributive shock, and cirrhosis.

As a compensatory response to hypoperfusion, the kidneys generate vasodilatory prostaglandins. Use of nonsteroidal antiinflammatory drugs (NSAIDs), which was seen in this patient, inhibits the production of vasodilatory prostaglandins, and thus, even a standard dose of NSAIDs can precipitate acute kidney injury in patients with renal hypoperfusion.[3]

Because the urine electrolyte levels were not measured in this patient, we cannot calculate the fractional excretion of sodium; a value of less than 1% would suggest a prerenal cause of acute kidney injury. However, the ratio of blood urea nitrogen to creatinine (each expressed in milligrams per deciliter) is often more than 20 in patients with a prerenal cause of acute kidney injury, and it was 12.5 in this patient. In addition, results of an examination of the urinary sediment are typically normal in patients with a prerenal cause of acute kidney injury, and they were abnormal in this patient. Finally, patients with a prerenal cause of acute kidney injury should have improvement in response to volume expansion, which restores renal perfusion; this patient's response to volume expansion was minimal. All these factors point away from a primary prerenal cause of acute kidney injury.[2]

INTRINSIC RENAL CAUSES OF ACUTE KIDNEY INJURY

Postinfectious glomerulonephritis is a common intrinsic cause of acute kidney injury in children, and it most often occurs after a group A streptococcal infection; however, poststreptococcal glomerulonephritis is more common in younger children than in adolescents, such as this patient.[4] Although the diarrhea, abdominal pain, and vomiting that were present in this patient may have been caused by an infection, pathogens that cause gastrointestinal infections are not typically associated with postinfectious glomerulonephritis. Other causes of rapidly progressive glomerulonephritis — such as anti–glomerular basement membrane disease, immune-complex disorders, or antineutrophil cytoplasmic antibody–associated vasculitis — are uncommon in children but should be considered in this patient, particularly since she had a family history of autoimmune disease. However, a patient with one of these glomerular diseases would be expected to have red-cell casts and dysmorphic red cells in the urinary sediment, and these features were absent in this patient.[3]

Acute interstitial nephritis, which is most commonly induced by drugs or infectious causes, is often (although not universally) associated with the presence of eosinophils or white-cell casts in the urinary sediment. However, the absence of these features and of fever, rash, and eosinophilia in this patient does not rule out acute interstitial nephritis. Although the use of NSAIDs can be associated with acute interstitial nephritis, this patient had taken NSAIDs only during the first 3 days of illness, and she had had no other exposure to medications that are known to trigger this disorder.

Another intrinsic cause of acute kidney injury is acute tubular necrosis, which is a consequence of prolonged acute kidney injury with a prerenal cause. In acute tubular necrosis, tubular ischemia leads to cell death and sloughing, which are associated with the presence of characteristic muddy-brown casts in the urinary sediment, a finding that was not seen in this patient.

Finally, vascular diseases, such as the hemolytic–uremic syndrome, should be considered. Such diseases result from damage to the micro-

vasculature in the kidneys, and they can be associated with anemia and thrombocytopenia, in addition to marked acute kidney injury.[5,6] All these features were present in this patient, and thus vascular disease is a leading consideration in this case.

ANEMIA

In the emergency department at the other hospital, laboratory testing did not reveal evidence of anemia, but the hematocrit decreased to 30.9% (normal range, 36.0 to 46.0) after the administration of 2 liters of normal saline. Classification of anemia according to the size of the red cells — microcytic, normocytic, or macrocytic — is often a helpful diagnostic approach. In this patient, the mean corpuscular volume was 73.0 fl (normal range, 78.0 to 102.0), which is consistent with microcytic anemia. Iron-deficiency anemia is the most common cause of microcytic anemia in adolescent girls, and additional laboratory testing might have clarified whether iron deficiency contributed to the anemia in this patient. However, other laboratory test results point toward an alternative explanation: the elevated lactate dehydrogenase level (10 times as high as the upper limit of the normal range) and the very low haptoglobin level indicate that a hemolytic process was present, despite the fact that hemolytic anemias are usually classified as normocytic.[7] Although this patient did not have an unusually high percentage of reticulocytes in the blood, a finding generally seen in patients with hemolytic anemia, it is possible that the renal release of erythropoietin may have been impaired in this patient because of her kidney disease.

THROMBOCYTOPENIA

Causes of thrombocytopenia can be divided into the following two main categories, which are defined according to the mechanism by which the platelet count is reduced: impaired platelet production and abnormal platelet destruction. In this patient, the presence of large platelets on a blood-smear examination suggests that the mechanism is more likely to be abnormal platelet destruction, because normally functioning bone marrow tends to produce large, immature platelets in response to the development of thrombocytopenia. Causes of abnormal platelet destruction include drug-induced processes, sequestration (particularly due to hypersplenism), immune-mediated processes, and disorders of consumption. This patient did not report a drug exposure that would put her at risk for thrombocytopenia, and she did not have evidence of splenomegaly on physical examination or ultrasonography. In addition, she did not have any signs or symptoms of thrombocytopenia (e.g., ecchymosis, petechiae, or nosebleeds), which are frequently present in patients with immune-mediated thrombocytopenia; her platelet count (53,000 per cubic millimeter) was higher than the count commonly seen in patients with immune-mediated disorders.[8] A process of consumption — such as disseminated intravascular coagulation, the hemolytic–uremic syndrome, or thrombotic thrombocytopenic purpura — remains possible. In these disorders, the vascular endothelium is disrupted, and thromboses that are rich in fibrin and platelets form in the microcirculation, consuming the platelets in peripheral blood.[9]

BLOODY DIARRHEA

Causes of bloody diarrhea can be separated into three broad categories: autoimmune causes (e.g., inflammatory bowel disease), anatomical causes (e.g., a bleeding Meckel diverticulum), and infectious causes. In this patient, the spontaneous resolution of bloody diarrhea after several days, taken together with her recent history of having eaten food purchased from street vendors, suggests that she most likely had an infectious process. Bacterial infections — including salmonella, shigella, yersinia, campylobacter, and Shiga toxin–producing *E. coli* — would be most common in this clinical scenario.[10] Although a stool culture was negative, the sensitivity of laboratory testing for the detection of enteric pathogens varies according to the timing of specimen collection and the type of laboratory evaluation that is performed, and thus, the negative culture does not rule out bacterial infection in this patient. For example, the detection of a serogroup of Shiga toxin–producing *E. coli* other than *E. coli* O157:H7 requires the performance of a culture-independent test for Shiga toxins or for the genes that encode them.

A UNIFYING DIAGNOSIS

I think this patient's illness involved an intrinsic renal disease that led to acute kidney injury, hemolytic anemia, consumptive thrombocytopenia, and infectious bloody diarrhea. The list of diagnoses that could be associated with all four

of these processes is relatively short — disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, systemic vasculitis, and the hemolytic–uremic syndrome — and it can be further narrowed on the basis of other features of the patient's clinical presentation.

Disseminated intravascular coagulation occurs in patients who have serious underlying conditions, such as sepsis, major injury, or cancer; this patient did not have any evidence of these conditions. Moreover, patients with disseminated intravascular coagulation usually present with signs of bleeding (e.g., petechiae, ecchymosis, or oozing from venipuncture sites), which were absent in this case. Patients with thrombotic thrombocytopenic purpura can present with a nonspecific prodrome that includes gastrointestinal symptoms, such as the prodrome seen in this patient, but the absence of purpura and neurologic symptoms and the severity of the acute kidney injury make thrombotic thrombocytopenic purpura unlikely in this case. The short timeline of this patient's illness lowers the likelihood of a systemic vasculitis; the illness began only 8 days before admission, and the patient had been previously healthy, with no history of fever, weight loss, joint pain, or rash.

The diagnosis that is most consistent with this patient's clinical presentation is the hemolytic–uremic syndrome, which is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Most cases of the hemolytic–uremic syndrome occur after infection (classically infection with Shiga toxin–producing *E. coli*); on rare occasions, the syndrome can occur as a complication of invasive infection with *Streptococcus pneumoniae*.[11] Other cases of the hemolytic–uremic syndrome are classified as atypical; these are mainly primary disorders of complement regulation that can be either sporadic or familial.[5,6,11]

The history of bloody diarrhea that began several days after the patient had eaten food purchased from street vendors might suggest a diagnosis of the hemolytic–uremic syndrome due to Shiga toxin–producing *E. coli*, but some features of this patient's illness would be unusual for this diagnosis. First, most children with this diagnosis are younger than 5 years of age.[6] Second, the bloody diarrhea that is associated with Shiga toxin–producing *E. coli* infection typically begins several days after the onset of watery diarrhea, but this patient had bloody diarrhea on the first day of illness.[10] Cases of atypical hemolytic–uremic syndrome can also be preceded by a triggering event, such as diarrhea,[12] and therefore, I would suggest not only testing for Shiga toxin (or genes encoding Shiga toxin) in the stool but also testing for the mutations in complement component genes that have been described in patients with atypical hemolytic–uremic syndrome.

One puzzling feature of this case was the absence of schistocytes on a blood-smear examination at the other hospital, since the presence of schistocytes would be expected in a patient with microangiopathic hemolytic anemia. Given how well the diagnosis otherwise fits this patient's illness, I wonder whether this result might have been spurious.

Dr. Virginia M. Pierce (Pathology): Dr. Klig, what was your impression when you evaluated this patient?

Dr. Jean E. Klig: When the patient arrived in the emergency department, we were presented with several clinical challenges. First, she had hypovolemia because of inadequate oral intake in the context of fluid loss due to prolonged diarrhea and vomiting. Second, despite the administration of antiemetic agents, she continued to vomit, possibly because of uremia in the context of rapidly declining renal function. Third, she had oliguric acute kidney injury, which we thought was most likely due to a combination of prerenal causes (volume depletion and NSAID use) and intrinsic renal disease, given the findings on urinalysis and ultrasonography. Fourth, the anemia, thrombocytopenia, and elevated serum aminotransferase levels had to be reconciled with the clinical features, which we thought were most likely caused by the hemolytic–uremic syndrome. Our primary goal was to restore renal perfusion without precipitating fluid overload and pulmonary edema. Therefore, we closely monitored the administration of an intravenous bolus of normal saline; afterward, the patient produced a small amount of urine.

Dr. Pierce: Dr. Sharma, what was your impression, and what were the next steps in this patient's treatment?

Dr. Amita Sharma: The patient's initial serum creatinine level was higher than would be expected in a patient with purely prerenal disease. The laboratory data suggested intravascular hemolysis with severe acute kidney injury. I thought that the patient may have had a combination of rapidly progressive glomerular disease and super-

imposed tubular damage. After the transfusion of platelets, a kidney biopsy was performed to aid in the diagnosis and prognostication of the renal involvement.

DR. ANN Y. KAO'S DIAGNOSIS

The hemolytic–uremic syndrome, probably atypical.

PATHOLOGICAL DISCUSSION

Dr. Kristen J. Tomaszewski: Shortly after the patient was admitted to the hospital, examination of a peripheral-blood smear revealed 2+ schistocytes. An enzyme immunoassay of a stool specimen for Shiga toxins 1 and 2 was negative. Histopathological examination of a kidney-biopsy specimen revealed evidence of thrombotic microangiopathy (Fig. 2A) and cortical tubular necrosis (Fig. 2B).

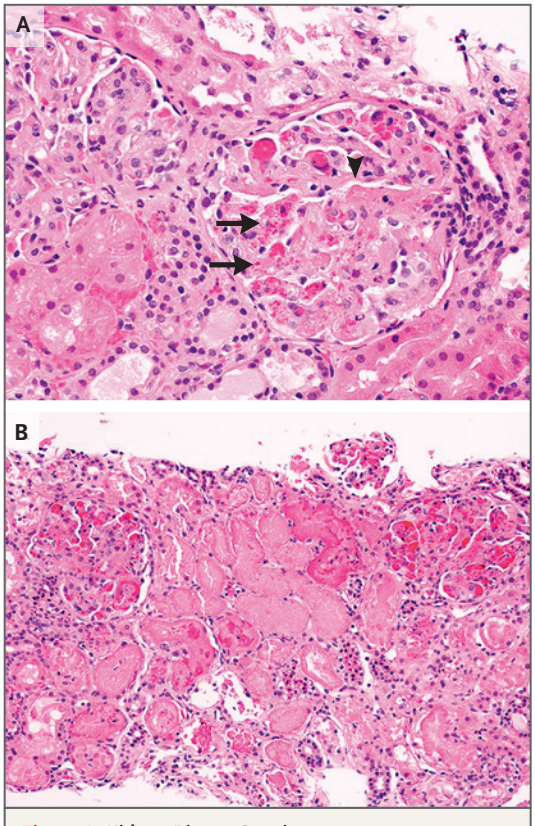

Figure 2. Kidney-Biopsy Specimen.
Hematoxylin and eosin staining of a kidney-biopsy specimen shows evidence of thrombotic microangiopathy, including fragmented red cells (Panel A, arrows) and fibrin deposition (Panel A, arrowhead), as well as tubular necrosis (Panel B).

An immunofluorescence assay and electron microscopy showed mesangial and intracapillary fibrin deposition; immune-complex deposits were not identified.

Although the presence of an acute glomerular thrombotic microangiopathy is consistent with the hemolytic–uremic syndrome, which was the leading clinical consideration in this patient, the differential diagnosis for the histopathological findings also included thrombotic thrombocytopenic purpura. To rule out thrombotic thrombocytopenic purpura, an assay for ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was performed; the result was 64% (normal range, ≥70). This mild reduction in ADAMTS13 activity is inconsistent with thrombotic thrombocytopenic purpura, which is often associated with levels of less than 10%, whereas mildly reduced ADAMTS13 activity may be present in patients with atypical hemolytic–uremic syndrome.[13] Another laboratory finding that is commonly seen in cases of atypical hemolytic–uremic syndrome is low activity in the alternative complement pathway, according to the AH50 assay, which indicates either a deficiency of an alternative or terminal complement pathway component or complement consumption. In this patient, the result of the AH50 assay was less than 10% (normal range, ≥46), which is consistent with atypical hemolytic–uremic syndrome.

A variety of mutations in complement component genes have been described in patients with atypical hemolytic–uremic syndrome. To identify the genetic underpinnings of this patient's disease, gene sequencing was performed at a reference laboratory; this testing included analysis for all known pathogenic variants in the *C3*, *C4BPA*, *C4BPB*, *MCP*, *CFB*, *CFH*, *CFHR1*, *CFHR3*, *CFHR4*, *CFHR5*, *CFI*, *DGKE*, and *THBD* genes; most of these genes encode alternative complement pathway components or inhibitors. Variants in these genes are identified in approximately 70% of patients with atypical hemolytic–uremic syndrome.[14] In this patient, a heterozygous *CFHR3* mutation of unknown significance (c.839_840delTA) was identified. This frameshift mutation results in the substitution of lysine for isoleucine at codon 280 in exon 6 of the *CFHR3* gene and ultimately results in a premature stop codon further downstream. The mutation is predicted to yield a decrease in (but not an absence of) CFHR3 protein expression; no data regarding the functional activity of

this variant have been published. Although this mutation has been described previously in a patient with atypical hemolytic–uremic syndrome, that patient reportedly had a CFHR3 deficiency, which was most likely due to a heterozygous deletion of *CFHR3–CFHR1* in conjunction with the mutation.[15] From a laboratory-medicine perspective, the cause of this patient's hemolytic–uremic syndrome remains undetermined.

DISCUSSION OF MANAGEMENT

Dr. Sharma: Atypical hemolytic–uremic syndrome is a clinical diagnosis that is supported by laboratory test results, and it should be considered when other causes of thrombotic microangiopathy have been ruled out. Among patients with atypical hemolytic–uremic syndrome, the prognosis is worse in those who have *CFH* mutations than in those who have *MCP* mutations or in those in whom the causative mutations are unknown. We speculate that the mutation that was identified in this patient may have interfered with CFH function or that she might have had an additional, unknown mutation.

Treatment with eculizumab, a humanized monoclonal antibody that binds to the C5 complement component and acts as a terminal complement inhibitor, was begun on the first hospital day. Because terminal complement inhibition is associated with a markedly increased risk of invasive meningococcal disease, meningococcal vaccines were administered before the initiation of this therapy. The patient had clinically significant uremia, fluid overload, and marked hypertension, and thus, hemodialysis was initiated. The urine output increased and results of renal-function tests improved after the first week, and dialysis was discontinued after six sessions. However, signs of hemolysis on laboratory testing took more than 6 weeks to resolve. While the patient was receiving dialysis, she underwent a blood transfusion.

In the absence of eculizumab treatment, the patient is at high risk for the development of end-stage renal disease,[12] and currently (6 months after presentation), she receives biweekly infusions of eculizumab. The result of the AH50 assay remains at less than 10%, but the soluble membrane attack complex level is normal. The current serum creatinine level is 0.6 mg per deciliter (53 μmol per liter), and she is normotensive, with normal results on examination of the urinary sediment.

FINAL DIAGNOSIS

Atypical hemolytic–uremic syndrome.

This case was presented at the Primary Care Pediatrics Conference, directed by Peter T. Greenspan, M.D., John Patrick T. Co, M.D., M.P.H., Ronni L. Goldsmith, M.D., Janice A. Lowe, M.D., and Benjamin A. Nelson, M.D.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Laurel Wickberg for assistance with conference organization, and Drs. Ivy A. Rosales, R. Neal Smith, and Robert B. Colvin for assistance with preparation of the pathological discussion.

REFERENCES

1. McCaffrey J, Dhakal AK, Milford DV, Webb NJ, Lennon R. Recent developments in the detection and management of acute kidney injury. Arch Dis Child 2017;102:91-6.
2. Andreoli SP. Acute kidney injury in children. Pediatr Nephrol 2009;24:253-63.
3. Whyte DA, Fine RN. Acute renal failure in children. Pediatr Rev 2008;29:299-306.
4. Blyth CC, Robertson PW, Rosenberg AR. Post-streptococcal glomerulonephritis in Sydney: a 16-year retrospective review. J Paediatr Child Health 2007;43:446-50.
5. Cheung V, Trachtman H. Hemolytic uremic syndrome: toxins, vessels, and inflammation. Front Med (Lausanne) 2014;1:42.
6. Fakhouri F, Zuber J, Frémeaux-Bacchi V, Loirat C. Haemolytic uraemic syndrome. Lancet 2017;390:681-96.
7. Noronha SA. Acquired and congenital hemolytic anemia. Pediatr Rev 2016;37:235-46.
8. Bussel JB. Thrombocytopenia in newborns, infants, and children. Pediatr Ann 1990;19:181-5, 188-90.
9. Mele C, Remuzzi G, Noris M. Hemolytic uremic syndrome. Semin Immunopathol 2014;36:399-420.
10. Holtz LR, Neill MA, Tarr PI. Acute bloody diarrhea: a medical emergency for patients of all ages. Gastroenterology 2009;136:1887-98.
11. Walsh PR, Johnson S. Treatment and management of children with haemolytic uraemic syndrome. Arch Dis Child 2018;103:285-91.
12. Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol 2010;5:1844-59.
13. Feng S, Eyler SJ, Zhang Y, et al. Partial ADAMTS13 deficiency in atypical hemolytic uremic syndrome. Blood 2013;122:1487-93.
14. Anderson M. Report of aHUS/DDD genetic evaluation: sequencing results. Milwaukee: Blood Center of Wisconsin, August 10, 2017 (https://www.versiti.org/media-library/pdfs/diagnostic-labs/test/ahus_genetic_eval).
15. Abarrategui-Garrido C, Martínez-Barricarte R, López-Trascasa M, de Córdoba SR, Sánchez-Corral P. Characterization of complement factor H-related (CFHR) proteins in plasma reveals novel genetic variations of CFHR1 associated with atypical hemolytic uremic syndrome. Blood 2009;114:4261-71.