CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 23-2017: A 9-Day-Old Girl with Vomiting, Acidosis, and Azotemia

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PRESENTATION OF CASE

Dr. Katherine L. Tuttle (Pediatrics): A 9-day-old girl was admitted to this hospital because of nonbilious vomiting, acidosis, and azotemia.

The patient had been born at another hospital by induced vaginal delivery after 41 weeks 3 days of gestation. The pregnancy had been complicated by maternal obesity. The patient was placed with an adoptive family immediately after birth. Her birth mother had received prenatal care, and screening tests for gonorrhea, chlamydia, syphilis, human immunodeficiency virus, and hepatitis B virus had been negative; a screening test for immunity to rubella virus was positive, as was a screening test for group B streptococcal colonization. Spontaneous rupture of membranes, which occurred 2 hours before birth, revealed meconium-stained amniotic fluid, and five doses of penicillin were administered before delivery. The 1-minute and 5-minute Apgar scores were 8 and 9, respectively.

At birth, the weight was 3.9 kg (87th percentile), the length 51.5 cm (80th percentile), and the head circumference 36.5 cm (85th percentile); the vital signs and physical examination were normal. A diet of organic cow's milk–based infant formula with a probiotic was begun shortly after birth; the patient drank the formula avidly, and urine and stool output were normal for her age. The results of newborn blood-spot screening tests (i.e., a panel of tests for multiple congenital diseases, primarily inborn errors of metabolism) and screening tests for hearing ability and critical congenital heart disease were normal, and the patient received intramuscular vitamin K, erythromycin ophthalmic ointment, and a hepatitis B immunization before discharge.

Five days before this admission, at a routine pediatric examination, the patient's adoptive parents reported that she had been drinking 60 ml of formula every 3 to 4 hours, with some "spit ups," and that she produced four yellow-brown stools each day. She appeared well, with mild jaundice, and was scheduled to return 10 days later for another routine appointment.

One day before this admission, nonprojectile, nonbloody, nonbilious vomiting occurred after each feed. The baby was fussier and less active than usual and drank only 30 to 45 ml of formula per feed before falling asleep, as compared with the 90 to 105 ml per feed she had had the previous day. Her father called the pediatrician during the evening and was advised to take the baby to the emergency department at another hospital.

On presentation to the other hospital, the patient was alert and responded appropriately to physical examination. The temperature was 37.8°C, the pulse 120 beats per minute, the blood pressure 85/59 mm Hg, the respiratory rate 36 breaths per minute, and the oxygen saturation 100% while she was breathing ambient air. The weight was 3.5 kg. The anterior fontanelle was sunken; the remainder of the examination was normal. A lumbar puncture was performed. Samples of blood, urine, stool, and cerebrospinal fluid were obtained for culture. Tests for respiratory syncytial virus and rotavirus were negative. Blood levels of total protein, albumin, total bilirubin, direct bilirubin, and alkaline phosphatase were normal; other laboratory test results are shown in Table 1. Urinalysis revealed orange urine, with a pH of 5.0, a specific gravity higher than 1.030, 3+ protein, and 2+ bilirubin. A chest radiograph was normal. Multiple attempts to place an intravenous catheter were unsuccessful; ampicillin and ceftriaxone were administered intramuscularly, and an enteral electrolyte solution was administered through a nasogastric tube and did not cause vomiting. Early during the following day, the patient was transferred to the pediatric intensive care unit (ICU) at this hospital for further evaluation and treatment.

The patient had lived with her adoptive family in an urban area of New England since birth. Her biologic half-brother had autism and eczema and had undergone placement of tympanostomy tubes. The patient had no known exposure to sick persons.

On admission to this hospital, the results of physical examination were unchanged. A peripheral intravenous catheter was inserted, and a bolus of normal saline was administered, followed by a continuous infusion of 10% dextrose in water with 0.225% normal saline. The point-of-care blood glucose level was 84 mg per deciliter (4.7 mmol per liter; reference range, 60 to 100 mg per deciliter [3.3 to 5.6 mmol per liter]). Ampicillin and cefepime were administered intravenously. Tests for respiratory syncytial virus, metapneumovirus, adenovirus, and parainfluenza viruses were negative; other laboratory test results are shown in Table 1. The patient was fed a cow's milk–based formula, and vomiting recurred. Enteral feeding was stopped, the administration of intravenous fluid was continued, and vomiting ceased.

The next day, the physical examination was normal. The results of an acylcarnitine profile analysis were normal, as were the results of blood amino acid analysis, with the exception of an alanine level of 582 nmol per milliliter (reference range, 139 to 474). Other laboratory test results are shown in Table 1. Urinalysis revealed clear, yellow urine, with a pH of 6.0, a specific gravity of 1.008, and 1+ glucose. An electrocardiogram was normal.

Dr. Rene Balza: An upper gastrointestinal series showed severe spontaneous gastroesophageal reflux; there was no evidence of intestinal malrotation. Ultrasonography of the kidneys and bladder revealed mild pyelectasis in the left kidney and was otherwise normal; limited abdominal ultrasonography revealed no evidence of pyloric stenosis.

Dr. Tuttle: The cultures of blood, urine, stool, and cerebrospinal fluid that had been performed at the other hospital remained negative, and ampicillin and cefepime were discontinued. Oral administration of an electrolyte solution was begun and did not cause vomiting.

On the third hospital day, the patient was transferred to the pediatric unit. Her home diet of an organic cow's milk–based formula with a probiotic was resumed. Overnight, she vomited once, approximately 2 hours after a feed. Vomiting after feeds continued during the next day. A diet of an oral electrolyte solution was resumed, and vomiting ceased. On the fifth hospital day, oral administration of an amino acid–based formula was begun and did not cause vomiting. The results of repeat newborn blood-spot screening tests were reported as normal; other laboratory test results are shown in Table 1. Over the next 2 days, the patient continued to receive the amino acid–based formula without vomiting; the administration of intravenous fluid was stopped. Laboratory test results obtained on the sixth and seventh hospital days are shown in Table 1. The

Table 1. Laboratory Data.*

Variable	Reference Range, Age-Adjusted†‡	1 Day before Admission, Other Hospital	On Admission, This Hospital	Day 2, This Hospital	Day 5, This Hospital	Day 6, This Hospital	Day 7, This Hospital	On Readmission, 3 Days after Discharge, This Hospital
Blood								
Hematocrit (%)	42.0–66.0	50.6 (ref 39.0–67.0)	43.8					40.8
Hemoglobin (g/dl)	13.5–21.5	18.1 (ref 12.5–22.5)	15.8					15.5
White-cell count (per mm^3)	5000–21,000	10,500	13,770					26,790
Differential count (%)								
Neutrophils	30–48	26.0 (ref 30.0–60.0)	29.0					50.0
Band forms		11.0 (ref 7.0–16.0)						
Lymphocytes	40–81	33.0 (ref 36.0–50.0)	46.0					29.0
Monocytes	4–11	26.0 (ref 4.7–12.0)	22.0					18.0
Eosinophils	0–8	4.0 (ref 0–3.0)	2.0					1.0
Metamyelocytes	0		1.0					2.0
Platelet count (per mm^3)	150,000–400,000	Platelet clumps present, count appears normal (ref 140,000–440,000)	377,000					628,000
Red-cell distribution width (%)	11.5–16.0	18.3	18.2					18.1
Description of peripheral-blood smear			Elliptocytes present, 1+ teardrops, large platelets present					Schistocytes, teardrops, and large platelets present
Sodium (mmol/liter)	135–145	141 (ref 133–145)	143	137	148	133	133	141
Potassium (mmol/liter)	4.0–5.6	4.1 (ref 4.1–5.3)	4.2	2.4	4.3	4.3	4.8	2.8
Chloride (mmol/liter)	98–106	116 (ref 98–115)	110	102	112	99	101	106
Carbon dioxide (mmol/liter)	19–22	7 (ref 13–22)	10	16	17	19	14	6
Anion gap (mmol/liter)	3–17	18 (ref 7–20)	23	19	19	15	18	29
Osmolality (mOsm/kg of water)	275–295					271	281	
Calcium (mg/dl)	8.5–10.5	11.5 (ref 7.6–10.4)	10.6	10.4		10.2	10.7	11.0
Phosphorus (mg/dl)	4.5–9.0		6.1	3.7		5.2	6.2	9.1
Magnesium (mg/dl)	1.7–2.4		2.1	1.6		1.6	1.7	2.1
Urea nitrogen (mg/dl)	5–20	47 (ref 4–18)	44	12		5	13	76

Creatinine (mg/dl)	0.30–1.00	1.11	0.75	0.38		<0.17	<0.17	1.77
Glucose (mg/dl)	60–100	103 (ref 65–99)	112	109	91			129
Alanine aminotransferase (U/liter)	7–33		55	126				17
Aspartate aminotransferase (U/liter)	47–150		57	57				20
Ammonia (μmol/liter)	12–48		82	55				
Creatine kinase (U/liter)	40–150			311				
Lactic acid (mmol/liter)	0.5–2.2			4.1	1.9			1.8
Pyruvate (mmol/liter)	0.08–0.16			0.29				
Venous blood gases								
Fraction of inspired oxygen			0.21		Unspecified			
Base excess (mmol/liter)	0–3.0		–12.9		–3.0			
pH	7.30–7.40		7.24		7.42			
Partial pressure of carbon dioxide (mm Hg)	38–50		32		33			
Partial pressure of oxygen (mm Hg)	35–50		43		98			
Arterial blood gases								
Fraction of inspired oxygen				Unspecified				
Base excess (mmol/liter)	0–3.0			–6.8				
pH	7.35–7.45			7.41				
Partial pressure of carbon dioxide (mm Hg)	30–35			26				
Partial pressure of oxygen (mm Hg)	60–80			114				
Urine								
Sodium (mmol/liter)						<10		
Potassium (mmol/liter)						6.3		
Chloride (mmol/liter)						38		
Osmolality (mOsm/kg of water)						189		
Phosphorus (mg/dl)						35.9		
Urea nitrogen (mg/dl)						166		
Creatinine (mg/dl)						30		

Table 1. (Continued.)

Variable	Reference Range, Age-Adjusted†	1 Day before Admission, Other Hospital	On Admission, This Hospital	Day 2, This Hospital	Day 5, This Hospital	Day 6, This Hospital	Day 7, This Hospital	On Readmission, 3 Days after Discharge, This Hospital
Cerebrospinal fluid								
Color		Slightly xanthochromic (ref colorless)						
Turbidity		Clear (ref clear)						
Red-cell count (per mm^3)								
Tube 1		36 (ref 0–3)						
Tube 4		8 (ref 0–3)						
White-cell count (per mm^3)								
Tube 1		4 (ref 0–5)						
Tube 4		4 (ref 0–5)						
White-cell differential count in tube 4 (%)								
Lymphocytes		50 (ref 5–35)						
Monocytes		50 (ref 50–90)						
Protein (mg/dl)		70 (ref 15–45)						
Glucose (mg/dl)		75						
Gram's stain		No polymorphonuclear leukocytes, no organisms						

* The term ref denotes the reference range used at the other hospital. 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 magnesium to millimoles per liter, multiply by 0.4114. 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 glucose to millimoles per liter, multiply by 0.05551. To convert the values for ammonia to micrograms per deciliter, divide by 0.5872. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110.

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

patient was discharged home on the seventh hospital day, at which time the weight was 3.4 kg.

Three days after discharge, the patient was seen for follow-up by her pediatrician. Her parents reported that she had had five episodes of spitting up during the previous 24 hours, that she had appeared tired and pale, and that her oral intake had decreased, such that she had consumed only 5 to 25 ml of the amino acid–based formula per feed that day. She was also producing frequent loose, small-volume, greenish stools (10 in a 24-hour period); during the bowel movements, borborygmi were audible and the patient arched her back.

On examination, the patient appeared pale and sleepy but aroused during the examination. The temperature was 37.3°C, the pulse 132 beats per minute, and the weight 3.0 kg. The anterior fontanelle was sunken, the lips were dry, skin turgor was decreased, and the capillary refill time was between 2 and 3 seconds. The patient vomited once in the clinic. The point-of-care blood glucose level was 98 mg per deciliter (5.4 mmol per liter). The patient was fed an oral electrolyte solution and then was referred to the emergency department of this hospital.

On arrival at the emergency department, the patient was lethargic and her skin appeared ashen; she cried weakly and without tears. The temperature was 37.8°C, the pulse 166 beats per minute, the blood pressure 73/50 mm Hg, the respiratory rate 58 breaths per minute, and the oxygen saturation 98% while she was breathing ambient air. The remainder of the examination was unchanged. Samples of blood and stool were obtained for culture. Blood levels of total protein, albumin, globulin, total bilirubin, direct bilirubin, and alkaline phosphatase were normal; other laboratory test results are shown in Table 1. Urinalysis revealed clear, yellow urine, with a pH of 6.0, a specific gravity of 1.030, and 2+ protein by dipstick; on microscopic examination, there were 0 to 2 red cells per high-power field, 5 to 10 white cells per high-power field, and 5 to 10 hyaline casts per low-power field. The patient was admitted to the pediatric ICU.

A bolus of normal saline was administered intravenously, followed by a continuous infusion of 5% dextrose with sodium bicarbonate and potassium chloride. The patient received an oral electrolyte solution without vomiting.

Dr. Balza: The next day, a central venous catheter was placed; abdominal radiography, which was performed to assess its position, revealed an abnormal bowel-gas pattern with narrowing of the lumen and separation of the bowel loops, findings suggestive of bowel-wall thickening or ascites (Fig. 1A). Abdominal ultrasonography revealed fluid-filled bowel loops with thickened walls (measuring up to 3 mm in thickness), as well as a small amount of associated free intraperitoneal fluid in the right half of the abdomen (Fig. 1B and 1C).

Dr. Tuttle: Stools continued to be loose and were guaiac-positive. Enteral feeds were discontinued, and the administration of total parenteral nutrition was initiated. Pantoprazole, ampicillin, cefepime, and metronidazole were administered intravenously.

Over the next 2 weeks, additional diagnostic studies were performed, and a diagnosis was made.

DIFFERENTIAL DIAGNOSIS

Dr. Jason M. Shapiro: This 9-day-old full-term female infant, who was born without perinatal complications, presented with recurrent episodes of nonbilious, nonprojectile emesis. The most striking aspect of her clinical presentation is the degree of dehydration and acidosis associated with each episode. Although the patient ultimately had clinical and imaging evidence of enterocolitis, the symptoms present during the initial clinical encounters were nonspecific and could be attributed to myriad causes, including infectious, anatomical, metabolic, and inflammatory or allergic conditions.

INFECTIONS

Despite the absence of fever in this patient, the feeding problems, lethargy, and acidosis are consistent with manifestations of neonatal sepsis.[1] The most common pathogens that are implicated in sepsis that occurs in otherwise healthy full-term neonates include group B streptococcus, *Escherichia coli*, *Listeria monocytogenes*, herpes simplex virus, and enteroviruses. Although this infant's birth mother was appropriately treated with penicillin during labor after prenatal identification of group B streptococcal colonization, such administration of antibiotics does not decrease the infant's risk of group B streptococcal sepsis beyond the first week of life. This patient under-

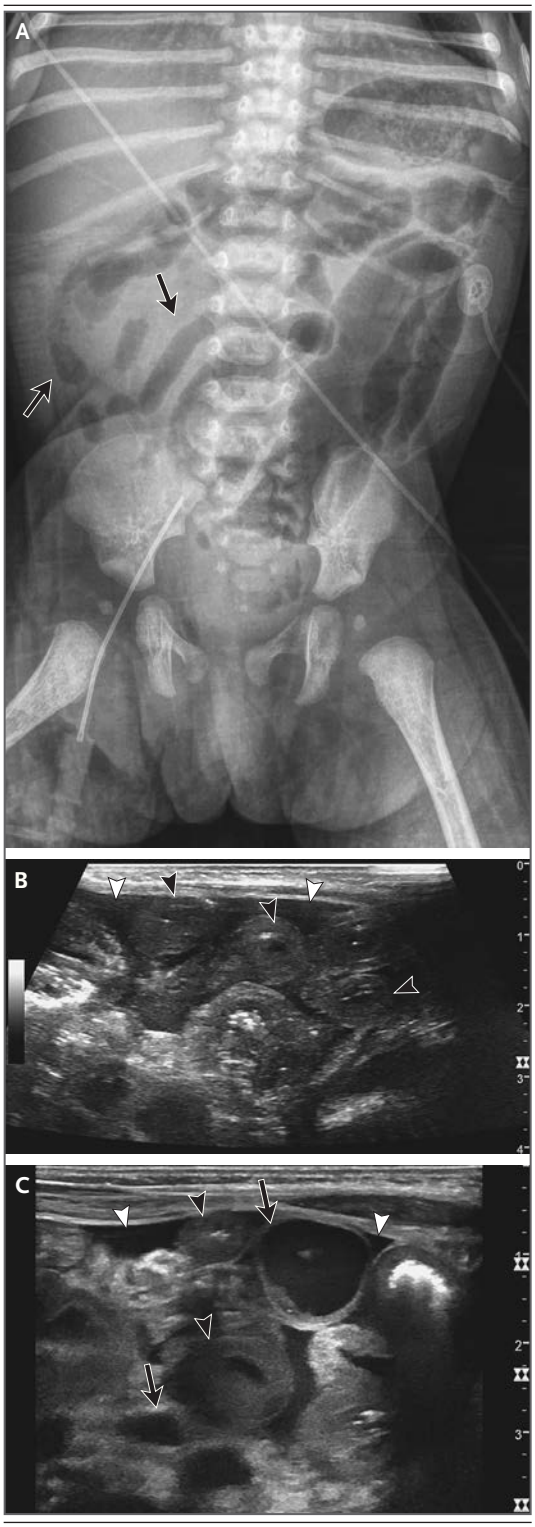

Figure 1. Imaging Studies.

An abdominal radiograph (Panel A) shows narrowing of the lumen and separation of bowel loops in the right half of the abdomen (arrows), findings suggestive of bowel-wall thickening. The bowel-gas pattern is nonobstructive, and air is seen in the distal colon. Abdominal ultrasound images obtained in a longitudinal view through the right lower quadrant (Panels B and C) show multiple loops of small bowel in cross section with areas of mural thickening (Panels B and C, black arrowheads) and areas of normal-appearing bowel wall (Panel C, arrows). Moderate ascites is also noted (Panels B and C, white arrowheads).

went an extensive albeit unrevealing evaluation for infectious causes, and an infection would be unlikely to explain all the features of her clinical presentation.

ANATOMICAL MALFORMATIONS

A variety of gastrointestinal anatomical abnormalities can result in intermittent vomiting and dehydration. In this patient, intestinal malrotation with intermittent midgut volvulus should be ruled out, and intestinal atresia or webs, pyloric stenosis, intussusception, and Hirschsprung's disease should all be considered. There was no history of polyhydramnios, and vomiting did not become apparent until 8 days of life; therefore, congenital intestinal or esophageal atresia is unlikely. Pyloric stenosis and intussusception can both result in recurrent vomiting, but these conditions are often seen in children who are older than this patient. Hirschsprung's disease is typically associated with the delayed passage of meconium; this infant passed meconium without difficulty within the first 24 hours of life, and thus this diagnosis is unlikely. The absence of gastrointestinal anatomical abnormalities on imaging studies is helpful in ruling out a gastrointestinal malformation as the cause of her presentation.

Renal anomalies and malformations of the central nervous system should also be considered in the differential diagnosis for a vomiting infant. I suspect the acute kidney injury in this patient was most likely a consequence of severe dehydration, but renal damage due to obstruction is another possible cause. However, abdominal ultra-

sonography revealed mild pyelectasis in the left kidney without hydronephrosis, a finding that rules out obstruction at the ureteropelvic junction. Although cranial imaging was not pursued, there was no history of neurologic deficits or macrocephaly that would specifically suggest hydrocephalus.

INBORN ERRORS OF METABOLISM

In an ill newborn with vomiting, dehydration, and profound acidosis, the possibility of inborn errors of metabolism warrants careful consideration. The newborn blood-spot screening tests are helpful in ruling out many of these conditions, but this panel of tests is not definitive, and further workup should be pursued if metabolic disease is clinically suspected.[2] In this case, the normoglycemia, normal muscle tone, and absence of hepatosplenomegaly, seizure activity, and dysmorphic features all argue against an inborn error of metabolism. However, several metabolic disorders are worth closer consideration.

Ornithine transcarbamylase deficiency is an X-linked defect of the urea cycle that is not detected on the routine newborn screening tests. The clinical presentation of ornithine transcarbamylase deficiency often involves lethargy, altered mental status, and vomiting, typically after feeds. The hallmark laboratory abnormality in patients with ornithine transcarbamylase deficiency or other urea-cycle defects is hyperammonemia, with ammonia levels often exceeding 150 μmol per liter (255 μg per deciliter). In this case, the patient is female, and the peak blood ammonia level was 82 μmol per liter (140 μg per deciliter); therefore, ornithine transcarbamylase deficiency is unlikely.

Aminoacidopathies and organic acidemias can lead to severe acidosis and vomiting. In addition, disorders of fatty acid oxidation can cause vomiting, lethargy, hypoketotic hypoglycemia, and resulting seizure activity. In infants with such disorders, symptom onset often occurs after a prolonged fast, since the condition results in an inability to fuel gluconeogenesis. This patient's symptoms occurred after feeds (rather than after fasting), and hypoglycemia and seizure activity were not observed. Furthermore, blood amino acid levels and an acylcarnitine profile were essentially within normal limits, and thus an inborn error of metabolism is unlikely.

INFLAMMATORY AND ALLERGIC CONDITIONS

During the second admission to this hospital, the infant had evidence of enterocolitis on imaging studies and guaiac-positive diarrhea. The differential diagnosis of these findings in a neonate includes necrotizing enterocolitis, very-early-onset infantile inflammatory bowel disease, and a non–IgE-mediated gastrointestinal food allergy. Necrotizing enterocolitis is a severe inflammatory disease of the intestine that is typically seen in premature infants. Less than 10% of cases occur in full-term infants, and in such cases, coexisting conditions such as perinatal tissue hypoxia, congenital heart disease, and endocrinopathies are commonly present.[3] Given that this infant had an uncomplicated full-term birth, the likelihood of necrotizing enterocolitis is low. Furthermore, imaging did not reveal pneumatosis, which is a characteristic finding of necrotizing enterocolitis, and stools were not reported to be grossly bloody.

Children younger than 6 years of age who present with clinical, imaging, endoscopic, or histopathological evidence of inflammatory bowel disease are considered to have very-early-onset disease. Although the incidence of very-early-onset inflammatory bowel disease is increasing, it remains exceptionally rare. Infants and children with this disease typically present with isolated colonic disease. Infantile inflammatory bowel disease is related to an underlying immunodeficiency in up to 25% of cases.[4,5] This patient had never had hematochezia and was noted to have a normal perianal examination. There was no evidence of an underlying immunodeficiency and no known family history of inflammatory bowel disease. Colonoscopy and histopathological examination of biopsy specimens could be helpful in ruling out very-early-onset inflammatory bowel disease, but the clinical presentation is not consistent with this condition.

Non–IgE-mediated food allergies — including food protein–induced enteropathy (FPE), food protein–induced allergic proctocolitis (FPIAP), and the food protein–induced enterocolitis syndrome (FPIES) — can occur in infants.[6] The most common trigger for these conditions is exposure

to milk or soy protein contained in infant formula. The inflammation associated with FPE is limited to the small bowel, and it results in malabsorption, vomiting, nonbloody diarrhea, and failure to thrive. FPIAP typically occurs during the first 6 months of life and accounts for 60% of cases of rectal bleeding in infants. Infants with FPIAP often appear well, and their symptoms resolve after the diet is switched to a partially hydrolyzed formula or an amino acid–based formula. FPIES is a severe non–IgE-mediated food allergy that can occur within the first few days of life on exposure to cow's milk–based or soy-based formula; this syndrome is unlikely to occur in exclusively breast-fed infants. The clinical presentation is often a combination of protracted emesis, diarrhea (often with guaiac-positive or grossly bloody stools), and severe dehydration. Up to 15% of infants with FPIES present with shock and need intensive care.[7] Laboratory findings in infants with FPIES are nonspecific and often include an elevated white-cell count (without peripheral eosinophilia), metabolic acidosis, hypoalbuminemia, and anemia. Imaging studies may show evidence of bowel-wall edema with intestinal air-fluid levels.

In this case, the initial decompensations were noted to occur after the infant received a cow's milk–based formula, there was a remote family history of atopy, and studies revealed leukocytosis, profound metabolic acidosis, and distended, fluid-filled bowel loops with thickened walls; all these features are consistent with a diagnosis of FPIES. The fact that this patient's condition deteriorated 5 days after her diet was transitioned to an amino acid–based formula does not rule out this diagnosis. Possible explanations for decompensation despite the switch to an elemental formula include accidental exposure to the previous cow's milk–based formula at home; a delayed T-cell–mediated hypersensitivity reaction, which results in a condition that has been described as chronic FPIES; or gradual progression of enterocolitis, which, in view of the results of subsequent imaging studies in this patient, was probably present before discharge from the first hospitalization. The diagnosis of FPIES is made clinically; it is based on the presence of characteristic symptoms and signs and on an improvement in the patient's condition after withdrawal of the triggering food.[8] After ruling out other potential causes, I think that the clinical history in this case suggests that FPIES is the most likely diagnosis.

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

Dr. Navneet K. Virk Hundal: When we initially evaluated this patient, the pattern of recurrent vomiting and lethargy after feeds, which improved when feeds were withheld or the diet was switched to an enteral electrolyte solution, prompted consideration of FPIES. During the second hospitalization, abdominal radiography revealed bowel-wall thickening with luminal narrowing; these findings raised concerns about enterocolitis, and therefore, we pursued esophagogastroduodenoscopy and flexible sigmoidoscopy in this patient. No gross abnormalities were noted during these procedures; mucosal biopsies of the esophagus, gastric antrum, duodenum, and rectum were performed.

CLINICAL DIAGNOSIS

Food protein–induced enterocolitis syndrome.

DR. JASON M. SHAPIRO'S DIAGNOSIS

Food protein–induced enterocolitis syndrome.

PATHOLOGICAL DISCUSSION

Dr. Lawrence R. Zukerberg: On histopathological examination, the esophageal-biopsy specimen appeared normal, without inflammation or intraepithelial eosinophils (Fig. 2A). In the gastric antrum, an increased number of eosinophils was seen in the lamina propria, with clusters of at least 10 eosinophils; occasional intraepithelial eosinophils were also present (Fig. 2B). The duodenum had normal villous architecture, an intact epithelium, and a normal brush border (Fig. 2C); the degree of chronic inflammation, including the number of eosinophils, in the lamina propria was normal. In the rectal-biopsy specimens, the number of eosinophils in the lamina propria was increased disproportionately to the number of other chronic inflammatory cells; high-power fields with more than 50 eosinophils were present (Fig. 2D).

Because eosinophils are a normal component

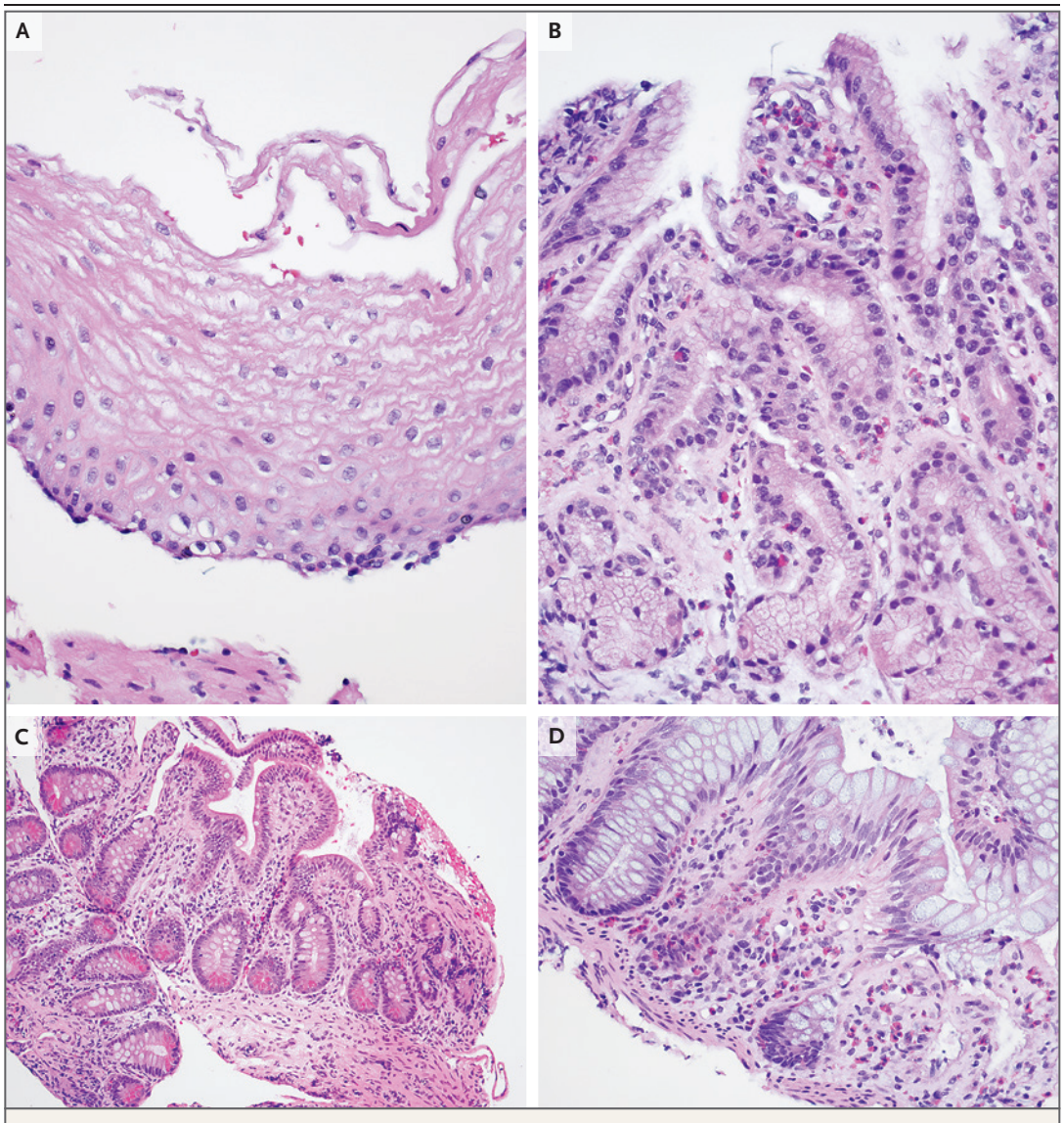

Figure 2. Gastrointestinal-Biopsy Specimens (Hematoxylin and Eosin).

In the esophagus, the squamous mucosa is normal in appearance (Panel A). In the gastric antrum, the mucosa contains a mildly increased number of scattered eosinophils in the lamina propria (Panel B). In the duodenum, the epithelium of the mucosa is normal in appearance; the chronic inflammation in the lamina propria, including the number of scattered eosinophils, is at a level that would be expected for this site (Panel C). In the rectum, the colonic mucosa contains an increased number of eosinophils in the lamina propria, as well as eosinophils infiltrating into the crypt epithelium (Panel D).

of chronic inflammation in the lamina propria, it can be difficult to know when they are indicative of disease. No intraepithelial eosinophils should be present in the esophageal mucosa, up to 2 eosinophils per high-power field should be present in the lamina propria in the stomach, up to 10 eosinophils per high-power field should be present in the small intestine, and fewer than 10 eosinophils per high-power field should be present in the rectum.[9] It is also important to note whether the number of eosinophils is disproportionate to the number of other inflammatory cells. In this case, eosinophils were abnormally numerous in the stomach-

and rectal-biopsy specimens and represented the predominant inflammatory cell.

These findings, in the absence of a hypereosinophilic syndrome or gastrointestinal eosinophilia triggered by such factors as a drug reaction or a parasitic infection, lead to an anatomical diagnosis of primary gastrointestinal eosinophilia or an eosinophil-associated disorder of the gastrointestinal tract. Histologic features of an eosinophilic gastrointestinal disorder are expected to be present in patients with FPIES[10,11]; on the basis of the features of this patient's clinical presentation, FPIES is the most likely diagnosis in this case.

DISCUSSION OF MANAGEMENT

Dr. Paul E. Hesterberg: After several days of bowel rest, the metabolic abnormalities and watery diarrhea improved in this patient. On the 17th hospital day, an enteral electrolyte solution was reintroduced without complication. Among patients in whom the use of a cow's milk–based formula results in FPIES, the use of a soy-based formula is also associated with a high rate of FPIES, and therefore, an extensively hydrolyzed casein (EHC)–based formula is recommended.[12] However, 10 to 15% of infants in whom the use of cow's milk–based formula results in FPIES will also have persistent symptoms with use of an EHC-based formula[13]; this was true for this patient, in whom an increased frequency of guaiac-positive stools with mucus quickly developed after the introduction of an EHC-based formula. On the 21st hospital day, an amino acid–based formula was reintroduced; the patient received the formula without complication, and the volume of formula was increased slowly over a 2-week period. The patient was discharged on the 44th hospital day with a long-term plan for absolute avoidance of dairy and soy protein.

Current recommendations for the management of FPIES include the avoidance of trigger foods for a minimum of 12 to 18 months after a reaction occurs.[12] This patient was seen in the clinic for follow-up at 11 weeks of age, at which time she had been receiving the amino acid–based formula without complication and gaining weight appropriately. Solid foods were introduced into her diet when she was between 4 and 6 months of age, beginning with fruits and vegetables and advancing to various grains, egg, nut butters, and meats.

Although FPIES is a non–IgE-mediated food allergy, up to 25% of patients with FPIES also have an IgE-mediated sensitization to the foods that triggered the initial reaction, and some will have symptoms of immediate hypersensitivity on exposure to the food.[13] Such patients have delayed resolution of FPIES.[14] At this patient's most recent follow-up visit, which took place when she was 1 year of age, skin-prick testing for allergies to both milk and soy extracts was positive. Skin testing or serum-specific IgE testing will be repeated before an oral food challenge is considered.

FINAL DIAGNOSIS

Food protein–induced enterocolitis syndrome.

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