CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 3-2012: A Newborn Boy with Vomiting, Diarrhea, and Abdominal Distention

Elliot Melendez, M.D., Allan M. Goldstein, M.D., Pallavi Sagar, M.D., and Kamran Badizadegan, M.D.

PRESENTATION OF CASE

Dr. Rebecca C. Bell (Pediatrics): A 6-day-old boy was admitted to this hospital because of vomiting, diarrhea, and abdominal distention.

The patient was born at another hospital to a teenaged primigravida by vaginal delivery after a full-term, uncomplicated gestation. The mother had received prenatal care; she had no history of sexually transmitted infections, and prenatal screening tests were negative. Meconium was present at delivery. The patient's birth weight was 4.3 kg (95th percentile), and the 1-minute and 5-minute Apgar scores were 7 and 9, respectively. Breast-feeding was initiated. The newborn passed two stools on the second day (the first at 30 hours of age). The next day, he reportedly had one loose, green stool. He was discharged home at 50 hours of age. He lived with his mother and her parents. When he was 3 and 4 days of age, he vomited yellow-green emesis on several occasions. He was otherwise well and breast-feeding regularly. At 3 a.m. on the day of admission, he became fussy and did not complete his normal feeding. Between 3 a.m. and 9 a.m., approximately six episodes of vomiting (initially breast milk, followed by mucus) occurred, with increasingly foul-smelling emesis. Diarrhea developed, and urine output decreased. Later that morning, he became less active; abdominal distention developed, and he stopped voiding. He was taken to a clinic affiliated with this hospital. On examination, he appeared tired, with intermittent grunting. The rectal temperature was 38.0°C. The abdomen was distended and tender, with hypoactive bowel sounds; stool was positive for occult blood. He was transported by ambulance to the emergency department of this hospital.

On examination, the patient appeared alert and slightly uncomfortable. The temperature was 37.2°C, the pulse 160 beats per minute, the respiratory rate 30 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. The weight was 3.9 kg. The abdomen was distended, soft, and tympanic, with decreased bowel sounds. There were small, bilateral noncommunicating hydroceles. The remainder of the examination was normal. A stool specimen showed no occult blood. Urinalysis revealed clear orange urine, with a specific gravity greater than 1.030, pH 6.5, nitrites, 1+ urobilinogen, 3+ bilirubin, 2+ albumin, and trace white cells, blood, glucose, and ketones. Urinalysis also revealed 0 to 2 red cells, 3 to 5 white

From the Department of Pediatrics, Children's Hospital (E.M.); the Departments of Pediatrics (E.M.), Surgery (A.M.G.), Radiology (P.S.), and Pathology (K.B.), Massachusetts General Hospital; and the Departments of Pediatrics (E.M.), Surgery (A.M.G.), Radiology (P.S.), and Pathology (K.B.), Harvard Medical School — all in Boston.

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cells, moderate bacteria, and a few squamous and renal tubular cells per high-power field. Ampicillin, gentamicin, and boluses of normal saline were administered. Other test results are shown in Table 1. Radiographs of the abdomen showed dilated loops of bowel in the lower abdomen, which were suggestive of distal bowel obstruction. There was no free air. An upper gastrointestinal series showed severe gastroesophageal reflux without evidence of malrotation. An enema administered with a water-soluble contrast agent revealed free flow of contrast material, with a long segment of narrowing involving the rectum and distal sigmoid colon and proximal distention of the descending colon. No stricture was identified. Rectal examination performed after the enema did not reveal blood or mucus. After the enema, the patient passed multiple nonbloody stools, and the abdominal distention decreased.

Seven hours after arrival in the emergency department, the temperature rose to 38.7°C; acetaminophen was administered. Lumbar puncture was performed; analysis of cerebrospinal fluid is shown in Table 2. Acyclovir was administered. The patient was admitted to the pediatric service. Shortly after admission, the temperature rose to 39.1°C and the pulse to 179 beats per minute, with poor capillary refill. He was transferred to the pediatric intensive care unit. Vancomycin and additional crystalloid were administered intravenously. During the first day, increasing abdomi-

Table 1. Laboratory Data.*

Variable	Reference Range, Age-Adjusted†	On Admission	2nd Hospital Day	3rd Hospital Day
Hematocrit (%)	45.0–67.0	66.0 (manual)	62.6	48.8
Hemoglobin (g/dl)	14.5–22.5		21.0	16.3
White-cell count (per mm^3)	9400–34,000	14,300	7000	6200
Differential count (%)				
Neutrophils	53–62	29	24	18 (ref 30–48)
Band forms	0–10	19		1
Lymphocytes	21–34	32	53	61 (ref 40–81)
Monocytes	4–11	15	17	18
Eosinophils	0–8		4	0
Basophils	0–3		1	2
Metamyelocytes	0	5	1	
Platelet count (per mm^3)	150,000–450,000	179,000	157,000	65,000
Sodium (mmol/liter)	135–145	138	136	140
Potassium (mmol/liter)	4.0–5.6	7.1 (hemolyzed)	3.5	3.5
Chloride (mmol/liter)	98–106	113	110	110
Carbon dioxide (mmol/liter)	19.0–22.0		17.1	22.5
Urea nitrogen (mg/dl)	5–20	46	34	19
Creatinine (mg/dl)	0.30–1.00		0.60	0.43
Glucose (mg/dl)	60–100	141	185	124
Bilirubin (mg/dl)				
Total	2.0–15.0		0.7	0.8
Direct	0.5–3.5		0.1	0.1
Protein (g/dl)				
Total	6.0–8.3		3.2	3.3
Albumin	3.3–5.0		1.6	1.9
Globulin	2.6–4.1		1.6	1.4

Table 1. (Continued.)

Variable	Reference Range, Age-Adjusted†	On Admission	2nd Hospital Day	3rd Hospital Day
Phosphorus (mg/dl)	4.5–9.0			3.0
Calcium (mg/dl)	8.5–10.5			7.3
Alanine aminotransferase (U/liter)	10–55		88	65
D-Dimer (ng/ml)	<500		2144	
IgG (mg/dl)	242–870			124
IgA (mg/dl)	2–52			<7
IgM (mg/dl)	19–82			7
IgE (IU/ml)	0–100			<5
Blood gas				
Source		Capillary	Arterial	Arterial
Fraction of inspired oxygen		0.21 (ambient air at sea level)	0.50	0.30
Base excess (mmol/liter)		–9.2	–8.8	2.1
pH	7.32–7.45 capillary, 7.35–7.45 arterial	7.29	7.35	7.51
Partial pressure of carbon dioxide (mm Hg)	35–50 capillary, 30–35 arterial	35	27	31
Partial pressure of oxygen (mm Hg)	40–90 capillary, 60–80 arterial	53	150	94
Bicarbonate (mmol/liter)	19–22	16	15	25

* Ref denotes the reference range at this hospital, adjusted for age. 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 bilirubin to micromoles per liter, multiply by 17.1. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for calcium to millimoles per liter, multiply by 0.250.

† 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.

nal distention, poor perfusion (as evidenced by cool extremities), and respiratory failure developed. A nasogastric tube was placed.

A continuous infusion of dopamine followed by norepinephrine was administered, and the trachea was intubated. Transthoracic echocardiography revealed a patent foramen ovale, a small patent ductus arteriosus with left-to-right shunting, and normal ventricular function. Stools became positive for occult blood, and perianal excoriation developed. Serum levels of lactate, aspartate aminotransferase, and alkaline phosphatase were normal; other test results are shown in Table 1. A repeat abdominal radiograph showed multiple distended loops of small bowel containing residual contrast material and relative decompression of the large bowel. Surgical consultants inserted a femoral central venous catheter and a radial arterial catheter. The administration of ampicillin was stopped, and meropenem was begun; pressors were adjusted to maintain a mean arterial pressure between 50 and 60 mm Hg.

Urine obtained by catheter on admission was cultured and grew few nonhemolytic streptococci (1000 to 10,000 colonies per milliliter; the streptococci were consistent with viridans group streptococci and were thought to be a contaminant); a blood culture was sterile. Screening of nasal specimens for respiratory viruses and enterovirus and of stool cultures for enteric pathogens and enterovirus was negative. On the third day, serum levels of lactate, magnesium, and ionic calcium were normal; other test results are shown in Table 1. Bicarbonate and immune globulin were administered intravenously. Total parenteral nutrition was begun.

Table 2. Analysis of Cerebrospinal and Peritoneal Fluid.*

Variable	Cerebrospinal Fluid		Peritoneal Fluid	
	Reference Range†	Day of Admission	Reference Range†	6th Day
Color and turbidity	Colorless, clear	Colorless, clear	Yellow, clear	Yellow, slightly turbid
White-cell count (per mm^3)			0–1000	1130 (11% neutrophils, 1% band forms, 81% lymphocytes, 1% monocytes, 6% plasma cells)
Tube 1	0–30	37 (29% lymphocytes, 71% monocytes)		
Tube 4	0–30	11 (2% neutrophils, 21% lymphocytes, 73% monocytes, 4% macrophage or lining cells)		
Red-cell count (per mm^3)			0	1585
Tube 1	0	21		
Tube 4	0	0		
Glucose (mg/dl)	50–75	120		
Protein (mg/dl)	5–55	48	Not defined	2200
Sodium (mmol/liter)			Not defined	139
Potassium (mmol/liter)			Not defined	3.2
Chloride (mmol/liter)			Not defined	105
Carbon dioxide (mmol/liter)			Not defined	32.2
Lactate dehydrogenase (U/liter)			Not defined	140
Amylase (U/liter)			Not defined	<3
Lipase (U/liter)			Not defined	26
pH			Not defined	7.46
Microbiologic tests		No organisms seen, culture sterile		No organisms seen, culture sterile
Enterovirus RNA (RT-PCR)	None detected	None detected		
Herpes virus nucleic acid (real-time amplification)	None detected	None detected		

* RT-PCR denotes reverse-transcriptase–polymerase chain reaction. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† 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.

During the first week, blood-pressure instability persisted and anasarca developed, with decreased urine output; dopamine, norepinephrine, albumin, and isotonic fluid boluses were administered. Vecuronium, fentanyl, and midazolam were given for sedation and analgesia. The platelet and red-cell counts decreased, and coagulation-test results showed a prolonged time to coagulation. Transfusions of platelets and red cells were administered, as was vitamin K. The serum level of C-reactive protein was 17.1 mg per liter (reference range for inflammation, <8.0); the level of alpha$_1$-antitrypsin in the serum was 137 mg per deciliter (reference range not defined) and in stool, 328 mg per deciliter (reference range, <55). Testing of stool for *Clostridium difficile* toxin, cultures of stool specimens for fungi and enteric pathogens, and culture of the urine for cytomegalovirus were negative. On the fifth day, the abdomen became mottled and tense, and the abdominal girth increased from 41 to 48 cm. An abdominal ultrasound examination revealed abundant ascites with septations that were worrisome for peritonitis. Paracentesis was performed, and peritoneal fluid (30 ml) was drained; results of fluid analysis are shown in Table 2. Intravenous fluid requirements gradually decreased, and the mean arterial pressure

and results of renal- and hepatic-function tests improved. Acyclovir and vancomycin were stopped, and furosemide was administered for gradual diuresis.

During the second week, the patient's vital signs and clinical condition gradually stabilized. Gentamicin and dopamine were stopped, norepinephrine was weaned, and gradual diuresis continued.

On the 14th day, a diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

EVALUATION AND MANAGEMENT OF NEONATAL SEPSIS

Dr. Elliot Melendez: All discussants are aware of the diagnosis in this case. This 6-day-old boy presented with signs of sepsis. Although viruses are the most common infectious cause of fever in infants, the prevalence of urinary-tract infection, bacteremia, and meningitis in patients less than 28 days old is between 8.8% and 13.3%.[1,2] For this reason, cultures from urine, blood, and cerebrospinal fluid were obtained. The most common bacterial pathogens are group B streptococci, *Escherichia coli*, and *Listeria monocytogenes*: thus, the administration of broad-spectrum antibiotics was initiated. Herpes simplex virus, a dangerous but potentially treatable virus, was considered, and the administration of acyclovir was initiated. Stool was reported as heme-positive in the clinic; it was heme-negative when the patient arrived at this hospital, but because of the abdominal distention, an abdominal source was considered. If bloody diarrhea is present, stool cultures for enteric bacterial pathogens must be sent. Appropriately, the neonate was admitted for observation and continuation of antibiotics pending culture results. On admission, he was recognized as having respiratory distress and cardiovascular dysfunction, as evidenced by poor capillary refill. He was transferred to the pediatric intensive care unit, where respiratory failure subsequently developed, and his condition met the consensus definition of severe sepsis.[3]

Severe sepsis with shock is associated with an imbalance between oxygen delivery and demand. The treatment strategy to correct this imbalance is referred to as early goal-directed therapy. Rivers et al.[4] found that in adults a sepsis algorithm with targeted goals in management can reduce mortality rates among patients with severe sepsis and shock. Unfortunately, in pediatrics, there are very little data on the use of early goal-directed therapy beyond aggressive fluid administration. Nevertheless, the principles of early goal-directed therapy are the same for both children and adults.

Oxygen was administered to improve oxygen delivery. If there are signs of respiratory insufficiency, early endotracheal intubation should be considered, as it was in this neonate. The history suggested the presence of absolute hypovolemia, probably due to increased insensible water losses from fever and tachypnea, as well as vomiting, diarrhea, and poor oral intake. Aggressive fluid resuscitation was given in the form of 0.9% saline in boluses of 20 ml per kilogram of body weight over a period of 5 to 10 minutes and repeated as long as signs and symptoms of shock persisted. Ringer's lactate would also have been acceptable. After the administration of 60 ml per kilogram, vasopressor therapy should be administered if the blood pressure remains low; however, more fluid can safely be given as long as there is no evidence of heart failure or volume overload.

Children are more likely than adults to have cardiac dysfunction in severe sepsis or shock, with 58% having low cardiac output and high systemic vascular resistance and 22% having both low cardiac output and low systemic vascular resistance.[5] As a result, because of its vasopressive and inotropic properties, the administration of dopamine was begun in this patient. The use of subsequent agents should depend on the clinical response and the predominant hemodynamic derangement. Because this patient had persistent shock with vasodilatation (warm shock), norepinephrine was subsequently added. Once the neonate was receiving dopamine and norepinephrine, an echocardiogram was obtained, which ruled out congenital heart disease.

Adequate control of fever can reduce metabolic activity and oxygen demand. Since some children have tachypnea or agitation, early control of the airway with sedation and analgesia, as was performed in this patient, can also be beneficial. Finally, prompt empirical treatment of infection can reduce the metabolic demand by the inflamed tissue.

Finally, a search should continue for a potential source of infection that can be controlled. Patients with infected indwelling foreign objects, such as central catheters, should have these objects

removed. Patients with necrotic wounds should undergo débridement. Abscesses should be drained, preferably by minimally invasive techniques. In this patient, who had progression of abdominal distention and development of bloody stools, an intraabdominal source of infection was likely, and we requested surgical consultation to assist with further evaluation and treatment.

BILIOUS EMESIS, LIQUID STOOLS, AND ABDOMINAL DISTENTION IN A NEONATE

Dr. Allan M. Goldstein: This neonate presented with bilious emesis, liquid stools, and abdominal distention. In the differential diagnosis of a potential intraabdominal process in this newborn, life-threatening conditions need to be considered first.

Intestinal Malrotation

Bilious emesis in newborns immediately raises concern for intestinal malrotation with midgut volvulus, a condition requiring prompt treatment. Abdominal distention and heme-positive diarrhea, as in this patient, can occur in malrotation with intestinal ischemia. A timely upper gastrointestinal series should be performed to rule out malrotation.

Necrotizing Enterocolitis

Necrotizing enterocolitis typically occurs in premature neonates, although 10% of cases occur in full-term neonates.[6] The onset of necrotizing enterocolitis in premature neonates is often delayed, but in full-term neonates it can develop within the first week of life.[6] Necrotizing enterocolitis is unlikely in this patient because of the absence of pneumatosis intestinalis on abdominal radiographs.

Enterocolitis Associated with Hirschsprung's Disease

Enterocolitis associated with Hirschsprung's disease (Hirschsprung's-associated enterocolitis) is a critical diagnosis that fits this newborn's presentation. Patients with Hirschsprung's disease, a congenital intestinal neuropathy characterized by the absence of ganglion cells extending from the rectum proximally for a variable distance, present with failure to pass meconium within 48 hours after birth and often progress to abdominal distention and vomiting.[7] In healthy newborns, 94 to 99% pass meconium by 24 hours, and 100% by 48 hours.[8,9] In newborns with Hirschsprung's disease, only 6% pass meconium by 24 hours,[7] and 37 to 54% by 48 hours[7,10] This patient first passed meconium at 30 hours of life, a finding consistent with Hirschsprung's disease. Vomiting, distention, loose stools, and fever occur, as in this patient, when Hirschsprung's disease is complicated by enterocolitis. In children with known Hirschsprung's disease, enterocolitis is the most serious complication. Even in infants and neonates without known Hirschsprung's disease, the diagnosis should be considered, since up to 12% of patients who are ultimately found to have Hirschsprung's disease present with enterocolitis.[11,12] Infectious gastroenteritis, allergic colitis (allergy to milk protein), and metabolic disorders are also possible in this patient but should be considered only after the critical diagnoses of Hirschsprung's disease and enterocolitis have been ruled out.

May we review the imaging studies?

Dr. Pallavi Sagar: Radiographs of the abdomen taken with the patient in the supine and decubitus positions (Fig. 1A and 1B, respectively) reveal dilated loops of bowel with air–liquid levels in the right abdomen, as well as a small-caliber rectum. These findings are worrisome for obstruction of the distal bowel. There is no free air or pneumatosis. An upper gastrointestinal series (Fig. 1C) shows severe, spontaneous gastroesophageal reflux. There is no evidence of malrotation. An enema administered with a water-soluble contrast agent (Fig. 1D) reveals free flow of contrast material from the rectum to the ascending colon without evidence of a stricture. There is narrowing of a long segment that has an irregular mucosal outline and involves the rectum and distal sigmoid colon, with reversal of the rectosigmoid index and a funnel-like transition into a dilated proximal sigmoid and descending colon. The transverse colon and ascending colon are also dilated. These findings are worrisome for distal bowel obstruction secondary to Hirschsprung's disease. The irregular mucosal outline may represent dyskinetic contractions of the aganglionic segment or colitis.

An abdominal ultrasonogram obtained on the fifth hospital day (Fig. 1E) shows abundant ascites with multiple internal septations, features of concern for peritonitis. Overall, these features suggest distal bowel obstruction, most likely due to Hirschsprung's disease, with colitis and peritonitis.

Dr. Goldstein: The findings on a barium enema examination — a contracted rectosigmoid with a

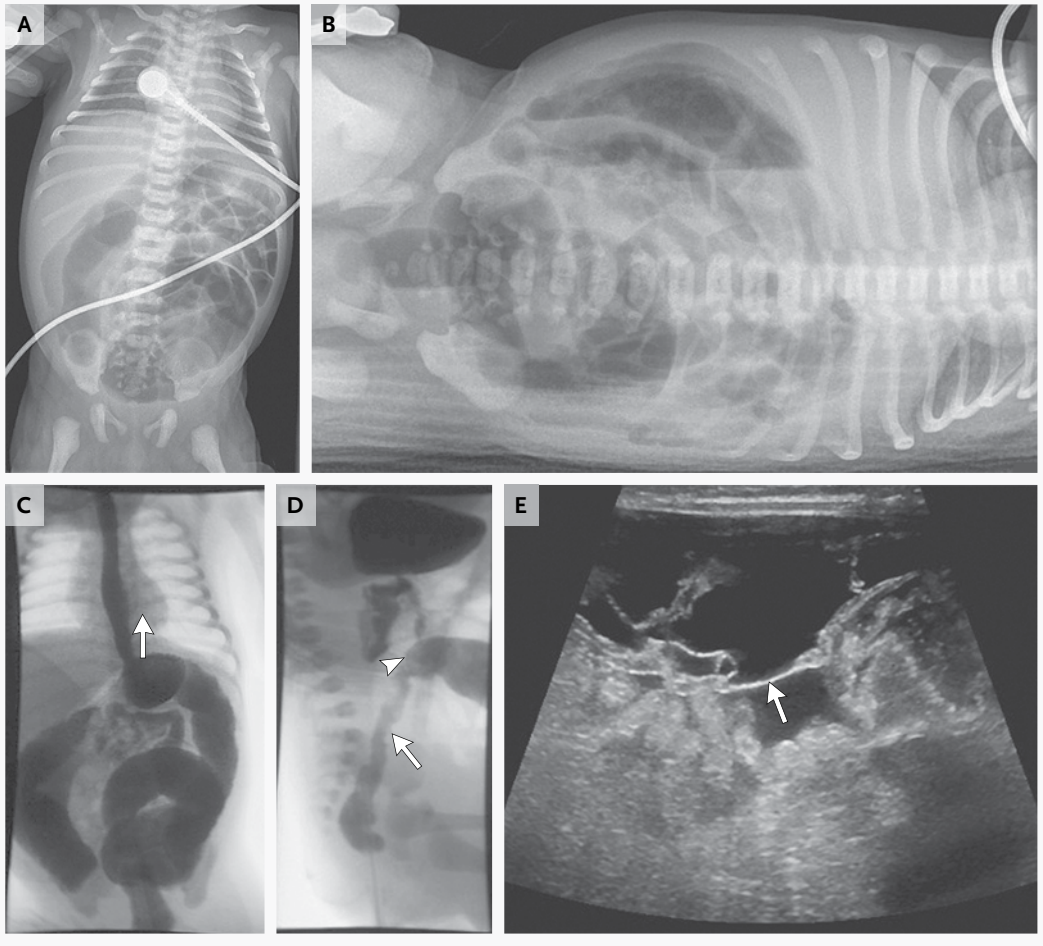

Figure 1. Radiographic and Ultrasound Images of the Abdomen.

Supine (Panel A) and left lateral decubitus (Panel B) views show dilated loops of bowel with air–liquid levels and without evidence of rectal air, features suggestive of distal bowel obstruction. There is severe spontaneous gastroesophageal reflux to the cervical esophagus (Panel C, arrow). An enema administered with a water-soluble contrast agent (Panel D) reveals narrowing of the rectum and sigmoid (arrow) with funnel transition to the descending colon (arrowhead). Mucosal irregularity of the narrowed segment suggests dyskinetic irregular contractions or colitis. An abdominal ultrasonogram (Panel E) shows ascites with internal septations (arrow) that are suggestive of peritonitis.

dilated descending colon — are characteristic of Hirschsprung's disease, and the sawtooth pattern of irregularity in the rectal mucosa is of concern for enterocolitis. These clinical and radiographic features all point to the diagnosis of Hirschsprung's disease with Hirschsprung's-associated enterocolitis. Prompt recognition and early treatment are essential. A definitive diagnosis of Hirschsprung's disease requires examination of a rectal-biopsy specimen to confirm aganglionosis. However, because of the acute inflammation in this patient, performing the biopsy needs to be deferred until the inflammation subsides, and treatment must be initiated on the basis of a presumptive diagnosis.

The incidence of enterocolitis in patients with Hirschsprung's disease varies widely, from 17% to 34%,[11-14] partly because of a lack of a standardized definition. Patients with Hirschsprung's-associated enterocolitis can present with symptoms ranging from mild abdominal distention with diarrhea to septic shock, as in this patient.[11,15,16] Lethargy and bloody stools can occur. Even mild diarrhea and abdominal distention in a patient with Hirschsprung's disease or in a neonate such as this one, with delayed passage of meconium, should

prompt consideration of Hirschsprung's-associated enterocolitis in order to avoid a delay in treatment and the associated complications. Hirschsprung's-associated enterocolitis remains the leading cause of death in patients with Hirschsprung's disease, although with increased awareness, earlier diagnosis, and improved management, the mortality rate associated with the disease has decreased from 33%[15] to approximately 1%.[13]

Management of Hirschsprung's-Associated Enterocolitis

Mild cases of Hirschsprung's-associated enterocolitis can be treated with oral metronidazole and rectal dilatation to relax the anal sphincter and allow the passage of stool. This patient presented with severe enterocolitis, which requires hospitalization, bowel rest, and broad-spectrum antibiotics that target bowel flora.[13] Rectal irrigation twice daily with 30 to 50 ml of warm saline applied through a flexible rectal catheter until the effluent is clear, performed to evacuate stool from the colon, is an important component of treatment.[15] Rectal irrigations or dilatations, which could have decreased the severity and duration of this patient's illness, were not performed. In patients whose condition does not improve with these measures, colostomy or ileostomy can be life-saving. This newborn's condition ultimately improved with aggressive medical support, and he did not require diversion.

After the enterocolitis resolves in this patient, tissue obtained by rectal suction biopsy should be examined to confirm the diagnosis of Hirschsprung's disease, and then definitive surgery should be planned to remove the aganglionic bowel. Despite definitive surgery, this patient is at risk for recurrence of enterocolitis. Recurrence occurs in 10 to 42% of patients; the reasons are unclear.[13,16-19] Trisomy 21 has been identified as a risk factor for Hirschsprung's-associated enterocolitis,[12,20] as have long-segment aganglionosis,[11,14] prior enterocolitis,[11,14] and anastomotic stricture.[21,22] Most important, the patient's family must be made aware of the early signs of enterocolitis and the importance of seeking prompt evaluation, and clinicians need to remain vigilant for this devastating Hirschsprung's-related complication.

DR. ELLIOT MELENDEZ'S DIAGNOSIS

Severe sepsis most likely due to an intraabdominal source.

DR. ALLAN M. GOLDSTEIN'S DIAGNOSIS

Hirschsprung's disease complicated by enterocolitis.

PATHOLOGICAL DISCUSSION

Dr. Kamran Badizadegan: The first diagnostic procedure was a suction biopsy that was performed to obtain rectal tissue. Alternative surgical procedures, such as deep mucosal or full-thickness rectal biopsies, may also be performed but often are not because of the increased risk of complications. The diagnosis of Hirschsprung's disease requires an adequate volume of the submucosa to confirm the absence of ganglion cells. In this case, the specimen was small, yielding fewer than 25 consecutive 5-μm sections with superficial submucosa (Fig. 2A). Criteria for specimen adequacy vary, although a mucosal-biopsy specimen measuring 2 to 3 mm in diameter and 1 mm in depth is generally considered adequate for diagnosis.[23] The diagnosis of Hirschsprung's disease is confirmed by the absence of ganglion cells on at least 75 consecutive 5-μm sections of tissue.[23] Thus, although no ganglion cells were identified, the small specimen precluded definitive evaluation for Hirschsprung's disease. A repeat biopsy was therefore recommended, and an adequate specimen was obtained (Fig. 2B), with no identifiable ganglion cells in 90 consecutive sections, a finding consistent with Hirschsprung's disease.

Ideal specimen size and technical quality are not always achieved; therefore, the diagnosis of Hirschsprung's disease is often supported by secondary or ancillary criteria, such as analysis of submucosal nerve fibers, histochemical staining for acetylcholinesterase, and immunostaining for calretinin. Hypertrophic submucosal nerves measuring more than 40 μm in diameter are highly characteristic of Hirschsprung's disease.[24] Although it is assumed that this finding represents compensatory hypertrophy of extrinsic nerves in the absence of intrinsic neurons, data to support this hypothesis are lacking. Support of the diagnosis in this case was provided by identification of hypertrophic submucosal nerves (Fig. 2B). Histochemical staining for acetylcholinesterase on frozen sections of mucosal-biopsy specimens in Hirschsprung's disease often reveals the presence of abnormal acetylcholinesterase-positive neurites

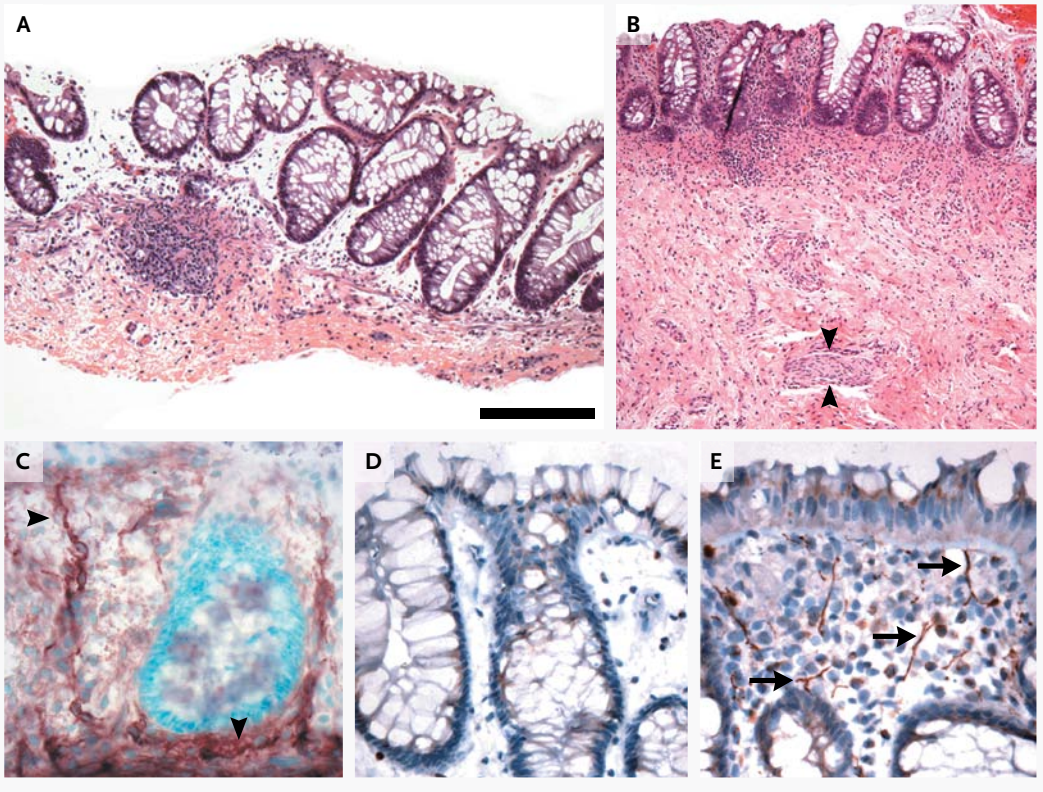

Figure 2. Suction-Biopsy Specimens of Rectal Tissue.

The original rectal tissue obtained with the use of a suction-biopsy instrument (Panel A, hematoxylin and eosin) did not show ganglion cells, but the biopsy specimen was considered too small for definitive diagnosis of Hirschsprung's disease. However, a specimen from the repeat suction biopsy (Panel B, hematoxylin and eosin) contained ample submucosa with no ganglion cells on more than 90 serial sections and markedly hypertrophic nerves (arrowheads). In addition, histochemical staining for acetylcholinesterase on an accompanying frozen-section slide (Panel C) highlighted thickened and irregular neurites within the lamina propria and the muscularis mucosae (arrowheads), supporting the diagnosis of Hirschsprung's disease. The original biopsy specimen (Panel A) was retrospectively immunostained for calretinin (Panel D) and showed a complete absence of calretinin-positive elements, a feature consistent with this diagnosis (immunoperoxidase stain for calretinin). Normal expression of calretinin-positive neurites is highlighted in a control specimen (Panel E, arrows; immunoperoxidase stain for calretinin). The solid bar represents 200 μm in Panels A and B, and 50 μm in Panels C, D, and E.

within the muscularis mucosae and has long been an invaluable ancillary technique. In this case, we identified abnormal acetylcholinesterase-positive neurites on a frozen-section slide (Fig. 2C). Studies published after this patient's diagnosis was established indicate that the absence of calretinin-positive mucosal neurites on immunohistochemical staining of paraffin sections is a highly sensitive marker for Hirschsprung's disease.[25,26] Calretinin is a calcium-binding protein that is normally expressed in cholinergic nerves; it is not known why calretinin-positive mucosal neurites are absent in Hirschsprung's disease and abnormal acetylcholinesterase-positive neurites are present. Retrospectively, the original suction-biopsy specimen was immunostained for calretinin and shows complete absence of calretinin-positive neurites (Fig. 2D and 2E). The availability of this stain may permit the diagnosis of Hirschsprung's disease on specimens that were previously considered inadequate.[25,26] There was no evidence of active colitis on either biopsy.

DISCUSSION OF MANAGEMENT

Dr. Goldstein: The biopsy in this case confirmed the diagnosis of Hirschsprung's disease. Definitive management requires resection of the aganglionic segment of colon, bringing normally in-

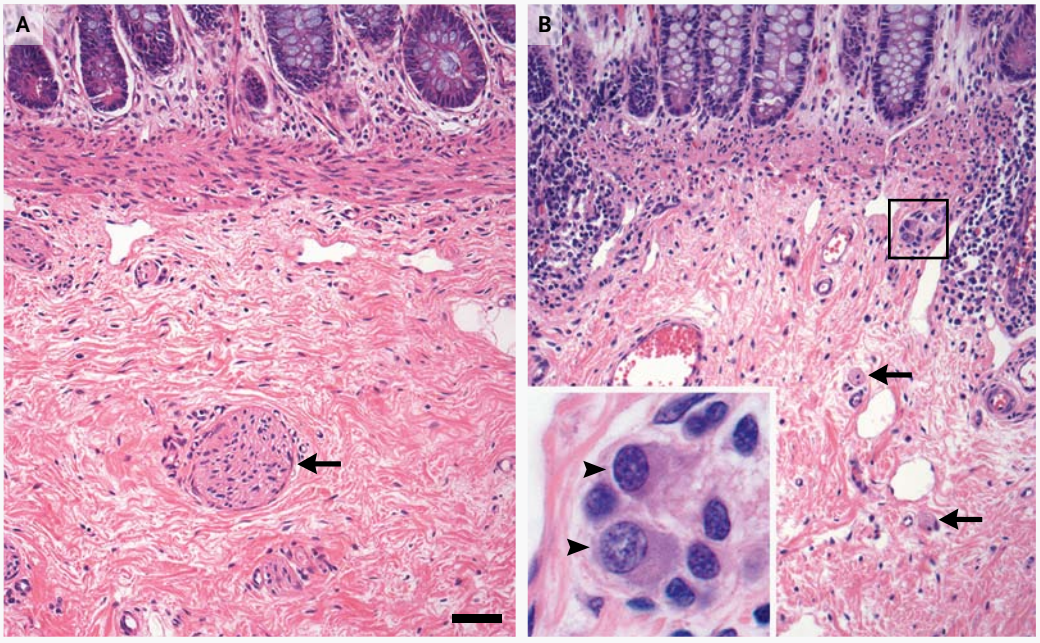

Figure 3. Rectosigmoid Resection Specimen (Hematoxylin and Eosin).

A representative photomicrograph of the mucosa and submucosa from the final rectosigmoid resection (Panel A) shows no ganglion cells and markedly hypertrophic submucosal nerves (arrow) in the distal half of the specimen. In contrast, the proximal half of the resection (Panel B) contains delicate submucosal nerve trunks (arrows) and readily identifiable ganglia (box). The area within the box is magnified in the inset to show two normal ganglion cells (arrowheads). The solid bar in Panel A represents 50 μm in Panels A and B, excluding the magnified inset.

nervated colon down to the anus, and the creation of a coloanal anastomosis. There are several options. One of the most common is called the Soave endorectal pull-through procedure, often performed as a one-stage operation entirely transanally, particularly for cases of short-segment disease limited to the rectosigmoid. When the aganglionosis extends proximal to the rectosigmoid, a combined transabdominal and perineal operation is performed. In some cases, a colostomy above the aganglionic segment (leveling colostomy) is performed first and the infant is brought back several months later for a definitive pull-through. This patient underwent a leveling sigmoid colostomy on hospital day 25. Three months later, he returned for a Soave endorectal pull-through procedure.

Dr. Badizadegan: At exploratory laparotomy, an obvious transition zone was seen in the sigmoid colon. The presence of ganglion cells proximal to the transition zone was confirmed on an intraoperative biopsy, and the patient underwent a Hartmann procedure, with end colostomy and a mucous fistula. Definitive resection with coloanal pull-through was performed approximately 3.5 months later. The specimen consisted of a segment of rectosigmoid that was 10 cm in length. Histologic sections from the distal half of the specimen (Fig. 3A) were distinctly different from those from the proximal half (Fig. 3B). Specifically, in the distal rectosigmoid, no submucosal or myenteric ganglion cells were seen and markedly hypertrophic submucosal nerves (up to 100 μm in diameter) were identified (Fig. 3A). However, in the proximal half of the specimen, ganglion cells were readily identified and submucosal nerves were normal in size (Fig. 3B). These findings confirmed the presence of a short segment of Hirschsprung's disease with an anatomically normal proximal resection margin.

Dr. Goldstein: This patient had multiple hospital admissions during the next 19 months for vomiting, diarrhea, and abdominal distention, often in the context of viral or bacterial illnesses, a course that is common in children with Hirschsprung's

disease, whose intestinal tracts seem particularly sensitive to any perturbations. It is often difficult to determine whether the symptoms are due to gastroenteritis or enterocolitis. However, it is better to assume that it is enterocolitis and treat with antibiotics and rectal irrigations or dilatations, since enterocolitis can progress rapidly, as was seen in this newborn. This case emphasizes that, even after the aganglionic colon has been removed, one must remain vigilant for the diagnosis of enterocolitis, since the risk persists.

Dr. Nancy Lee Harris (Pathology): Dr. Cronin, you are this patient's pediatrician. Would you tell us how he is doing?

Dr. Rebecca M. Cronin (Pediatrics): This patient is now 2 years old and is doing well medically, despite all his hospital admissions. The primary care of a patient such as this one with a chronic medical illness requires educating the family about the potential complications of this illness and the potential for recurrence. Although the patient's mother is very young, she has done remarkably well caring for him and has brought him promptly to medical attention when necessary. One issue this family has had to deal with is behavioral problems. Chronically ill and frequently hospitalized children are often seen as vulnerable, and it is hard for parents to consistently and appropriately discipline them. For example, toilet training for this patient is going to require consistent limit setting. Since lifelong constipation is a serious possible consequence of Hirschsprung's disease, establishing good bowel habits will be important to his overall health. We have involved child life specialists and early intervention specialists, who can help with developing good skills for parenting ill children.

Dr. Harris: Are these parents at risk for having another affected child?

Dr. Goldstein: Hirschsprung's disease is a multifactorial disorder with complex inheritance. The risk to a subsequent sibling is higher if the affected child is female or has long-segment disease. In this case, which involved a boy with short-segment aganglionosis, the risk of Hirschsprung's disease in a sibling is only 3 to 5%. Because of the low penetrance associated with a single gene mutation in nonsyndromic Hirschsprung's disease, the utility of genetic testing currently is limited.

Dr. Harris: Is there an algorithm in the neonatal units that would lead one to raise the question of Hirschsprung's disease early in the course?

Dr. Goldstein: The possibility of Hirschsprung's disease should at least be considered in a full-term neonate who does not pass a first meconium stool within 24 hours after birth.

ANATOMICAL DIAGNOSIS

Hirschsprung's disease with enterocolitis.

This case was discussed at Pediatric Grand Rounds.

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

Dr. Badizadegan is currently at Nemours Children's Hospital, Orlando, FL.

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