Necrotizing Enterocolitis and Milk Protein Intolerance

Causes of Rectal Bleeding in a Term Infant

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Both necrotizing enterocolitis and severe milk protein intolerance causing grossly bloody stools are uncommon in the term infant. Necrotizing enterocolitis is a disease primarily of premature, low-birthweight infants who have been significantly stressed. Milk protein intolerance is a common disease with a variety of manifestations, but diarrhea with gross blood loss is uncommon. A case is reported of an infant suffering from both diseases.

CASE REPORT

A 7-day-old infant was brought to the Family Medical Center with a history of bloody diarrhea. The mother had had an uncomplicated prenatal course and an uncomplicated, planned repeat cesarean section at 39 weeks' gestation. Apgar scores were 9 and 9 at 1 and 5 minutes for this 2,900-g infant. Findings on newborn examination were unremarkable. Feedings with infant formula (SMA) were begun in the newborn nursery. Blood was noted in the stool on the second day of life but was attributed to an anal fissure, and the child was discharged on the third day of life with mother changing the formula to Enfamil. Persistent diarrhea with bloody mucous was noted by the mother. Family history was remarkable for the mother, the maternal grandfather and the three siblings of the maternal grandfather, and the mother's cousin all having had milk protein intolerance and having required breast milk only or goat's milk.

On examination the infant was alert and responsive but had a 1-pound weight loss since birth, a pulse of 168 beats per minute, and bloody mucus on examination of the stool. The infant was admitted for further evaluation and treatment. The workup revealed necrotizing enterocolitis with right lower quadrant pneumatosis intestinalis visible on abdominal radiographs. Admission blood determinations included a white blood cell count of 35.0×10^9/L ($10^3/\mu$L) with a differential of 0.35 polymorphonucleocytes, 0.02 band cells, 0.45 lymphocytes, 0.15 monocytes and 0.02 eosinophils. Room air blood gas results revealed mixed metabolic acidosis and respiratory alkalosis (pH 7.39, pCO_2 16 mmHg, pO_2 66 mmHg). Treatment included nasogastric suction, bowel rest, antibiotics, and hyperalimentation. The workup for sepsis was negative, and stool cultures did not reveal pathogens.

On the 11th day of hospitalization oral feedings were resumed beginning with glucose water and advancing to infant formula (Similac). On the second day of feedings, abdominal distention and bloody stools were noted. Feedings were changed to a second infant formula (ProSobee) without improvement. Workup at this time did not show evidence of pneumatosis but did show an eosinophil count of 7.8×10^9/L, 0.28 of all leukocytes. The infant's feedings were changed to an oral electrolyte solution (Pedialyte) followed by a formula of hydrolyzed protein (Nutramigen) and breast milk with resolution of symptoms. The in-hospital exacerbation was diagnosed as milk protein intolerance and not a recurrence of necrotizing enterocolitis. The patient was discharged at 22 days of life after 15 days of hospitalization. Follow-up barium enema showed no evidence of stricture or obstruction.

The infant did well until 28 days of age, at which time he presented to the Family Medical Center with emesis.

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Workup now revealed pyloric stenosis, which was treated with pyloromyotomy without complications.

DISCUSSION

Since its original description in 1891, the epidemiology of necrotizing enterocolitis has been studied and reviewed extensively.[1–4] The mechanism immediately responsible for the intestinal damage is probably ischemic necrosis precipitated by a variety of factors such as hypoxia, infection, and overfeeding. The majority of necrotizing enterocolitis cases occur in premature infants with newborns beyond 38 weeks' gestation comprising fewer than 5 percent of cases.[5] The incidence is in the range of 1 per 1000 and mortality rate is in the range of 40 percent. The three essential components for the development of necrotizing enterocolitis described by Santulli et al[2] are (1) injury to the bowel mucosa, (2) presence of bacteria, and (3) availability of metabolic substrate. (Necrotizing enterocolitis, however, has been found in unfed infants.[6] Term infants who develop necrotizing enterocolitis tend to do so in the first days of life in contrast to premature infants, who may develop the disease later.

Necrotizing enterocolitis may manifest itself with abdominal distention, emesis, and diarrhea with blood in the stools. Radiologic examination may reveal intramural air (pneumatosis intestinalis). The course may be fulminating and lethal. Breast milk may be protective, but Kliegman et al[7] did not find human milk to be effective in lowering necrotizing enterocolitis in high-risk infants.

Staging criteria have been used so that the rational comparisons between groups of patients with necrotizing enterocolitis can be made.[5] Hemorrhagic colitis may be part of the spectrum of necrotizing enterocolitis, but without other clinical or radiologic stigmata, necrotizing enterocolitis may be overdiagnosed in some instances.[8] Loose labeling of the infants with no manifestation of necrotizing enterocolitis other than blood in stools may in part explain differences in the reported incidences of necrotizing enterocolitis. As demonstrated by the in-hospital exacerbation of bloody stools in this case and documented in published series, bloody stools may be a manifestation of intolerance to cow's milk.[9–12]

Milk protein intolerance afflicts between 0.5 and 7.5 percent of the population.[13,14] Diagnosis is often clinical, but the presence of eosinophilia and confirmatory allergy testing may be helpful.[13] Heredity plays a significant role, with 60 percent of infants with milk protein intolerance having a positive family history.[15] Although the average age of presentation is 2 months, it has been noted as early as the first day of life.[16] The gastrointestinal tract, respiratory tract, and skin are most commonly affected, with

symptoms ranging from rhinitis, asthma, and urticaria to diarrhea with blood loss.[17]

Gastrointestinal manifestations of milk protein intolerance can occur anywhere from the stomach to the small bowel and colon, and symptoms may be acute or delayed. Gastric and duodenal lesions present with vomiting and occult blood loss. Small bowel lesions cause a presentation similar to celiac disease with vomiting, malabsorption, and failure to thrive. Colonic lesions may present with blood and mucus in the stool, abdominal distension, and emesis. Symptoms regress on a milk-free diet, and recur following a repeat milk challenge.[13] Soybean protein is recognized as having equal antigenicity with cow's milk protein, and infants having milk protein intolerance may at the same time have intolerance to soy-based formula.[13,16]

The exact pathophysiology of milk protein intolerance is unknown. Direct toxicity to the gastrointestinal mucosa by milk proteins or an exaggerated immunological response to milk proteins or both have been postulated. In neonates, increased gastrointestinal absorption of antigenic material leading to sensitization may result from gut immaturity or ischemic or inflammatory damage to the epithelium.[2] In this child it is unknown whether colonic damage secondary to necrotizing enterocolitis contributed to the development of milk protein intolerance, or whether the milk protein intolerance contributed to the development of necrotizing enterocolitis. This child's course was further complicated by pyloric stenosis, which does not appear related to either milk protein intolerance or necrotizing enterocolitis.

In the term infant the diagnosis of necrotizing enterocolitis may initially elude the unsuspecting physician, who may attribute the bleeding to a more benign cause. The possibility of milk protein intolerance may also be missed in the child with bloody stools. Physicians must maintain an index of suspicion for both common and uncommon causes of bleeding in the neonate. Prognosis may be significantly improved by early and aggressive therapy of these conditions.

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