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The purpose of this article is to review the differential diagnosis for rectal bleeding in the neonate and to discuss eosinophilic gastroenteritis as one possible cause.

Neonatal Eosinophilic Gastroenteritis: Possible In Utero Sensitization to Cow's Milk Protein

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EOSINOPHILIC GASTROENTERITIS (EG) IS AN UNCOMMON benign disorder manifesting with blood-streaked stools in otherwise healthy appearing infants who are breastfed or formula-fed.¹⁻³ It is a rare form of primary eosinophilic gastrointestinal disease (EGID), which is characterized by gastrointestinal (GI) symptoms, segmental infiltration of the GI walls with eosinophils, and variable peripheral blood eosinophilia in the absence of known causes for GI eosinophilia (e.g., drug reactions, parasitic infections, and malignancy).^{4,5} EGID includes eosinophilic esophagitis, eosinophilic gastritis, EG, eosinophilic enteritis, and eosinophilic colitis. The etiology of primary EGID remains largely unknown. Cow's milk protein (CMP) and soy proteins are the foods most frequently implicated

in the infantile form because most infants recover with a short period of bowel rest, parenteral nutrition, and subsequent feeding with CMP-free milk formula or breast milk from a mother who has excluded all dairy products from her diet.⁶⁻⁸ However, the condition has been described in infants exclusively breastfed.^{5,9} Symptoms usually appear during the first four weeks of life and resolve within 48-72 hours after the elimination of dietary CMP in the infant's formula or from the maternal diet.¹⁰

ABSTRACT

Rectal bleeding in neonates is an alarming sign that suggests a possible serious underlying condition, such as infection or bleeding disorder that would necessitate hospitalization and prompt intervention. We report a case of eosinophilic gastroenteritis caused by cow's milk protein allergy in a one-day-old infant, who presented with frankly bloody stools associated with massive gastrointestinal and peripheral blood eosinophilia prior to initiation of enteral feedings. The patient's outcome was favorable, with complete spontaneous recovery in one week, after a period of bowel rest, parenteral nutrition, and use of amino acid formula. The eosinophilia was also transient and gradually resolving by two months of age. Rectal bleeding secondary to allergic colitis caused by cow's milk sensitization may occur in neonates, and failure to appreciate this possibility may lead to inappropriate diagnostic or therapeutic intervention.

Keywords: eosinophilia; eosinophilic gastroenteritis; cow's milk protein allergy; neonatal; rectal bleeding

CASE STUDY

A 37-week-gestation male infant was born to a 31-year-old, G2P2, mother with unremarkable serology results except for a positive GBS screen and possible history of celiac disease. The

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infant was delivered by elective, repeat cesarean section with Apgars of 8 and 9 at one and five minutes, respectively. Amniotic fluid at birth was described as “dark with hint of pink” and was thought to be meconium-stained fluid by the obstetrician. He required no resuscitation and was transferred to the well-infant nursery for routine care. Upon admission, Baby E was noted to have bloody gastric aspirates and started to pass bloody stools at two hours of age, prior to initiation of enteral feedings.

The infant has a normal newborn examination with a soft, nondistended, nontender, nondiscolored abdomen. No anal fissures were noted to account for the bleeding. His skin was pale, poorly perfused with capillary refill of four to five seconds, and no exanthem. The rest of vital signs were within normal limits. His abdominal radiograph revealed normal gas pattern with no pneumatosis intestinalis, or free air. Admission laboratory tests (Table 1) demonstrated mild anemia and eosinophilia in complete blood count (CBC) secondary to rectal bleeding and inflammatory process in the GI tract. Stool microscopy revealed numerous leukocytes, with abnormal elevated eosinophils up to 71 percent, and low serum total protein and albumin.

GI endoscopy was carried out on the third day of life (DOL) for direct visualization of the mucosa of the GI tract, to identify the site of bleeding and to obtain tissue biopsies. Upper GI endoscopy revealed erythema in the stomach and duodenum, with somewhat flat duodenal folds (Figure 1A). Sigmoidoscopy revealed erythema and small aphthous ulcers

in the rectosigmoid region (Figure 1B). Figure 2 shows normal colonoscopic and sigmoidoscopic findings from another patient for comparison. Histological examination showed eosinophilic infiltration in the esophagus, stomach, duodenum, and sigmoid colon (Figure 3).

A bone marrow aspiration and biopsy was carried out because of the possibility of malignancy but showed no evidence of malignancy. Acute leukemia and myeloproliferative neoplasms were further ruled out with fluorescent in situ hybridization (FISH). The rare leukemic or myeloproliferative neoplasms associated with eosinophilia are often associated with characteristic cytogenetic rearrangements involving either fibroblast growth factor receptor 1 (FGFR1), platelet-derived growth factor receptor alpha (PDGFR α), or platelet-derived growth factor receptor beta (PDGFR β). None of the classic cytogenetic aberrations were detectable by FISH, essentially ruling out an underlying malignant process as the etiology of this patient’s eosinophilia. Idiopathic hypereosinophilic syndrome (HES), a diagnosis of exclusion, presents with multisystem organ toxicity because of eosinophilic infiltration. Echocardiogram and cranial and abdominal ultrasounds were all normal in this patient, making this diagnosis unlikely.

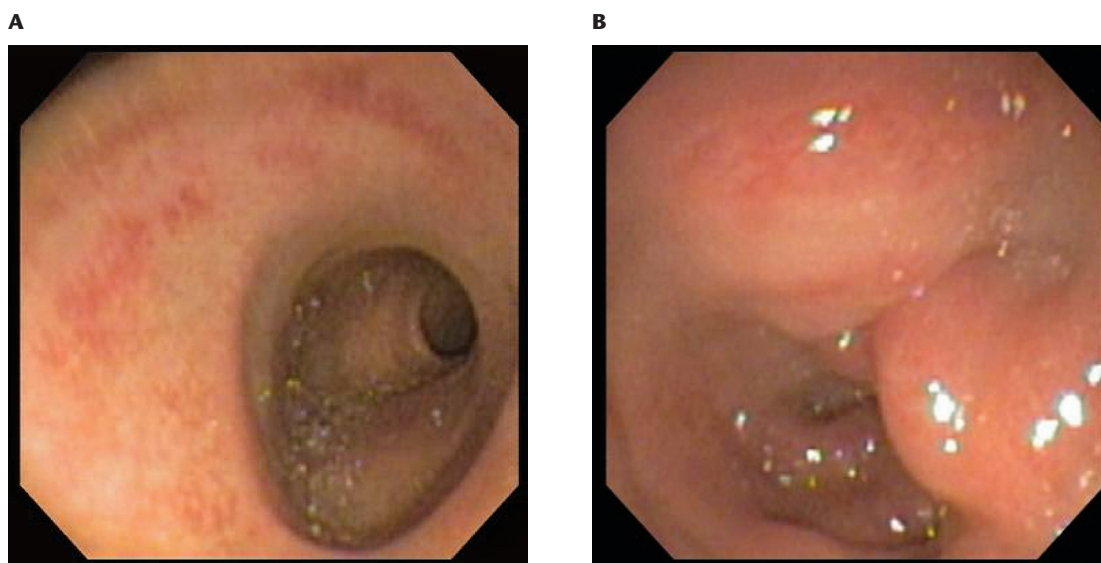
Serial white blood cells (WBCs; Table 2) showed peaked eosinophilia on DOL 6, gradually resolving to normal by the end of the first month of life, even after reintroduction of breast milk and after elimination of all foods that contain cow’s milk from the mother’s diet.

TABLE 1 ■ Admission Laboratory Tests

Test	Indication to Look For	Findings		Interpretation
CBC with differential	Evidence of infection, anemia, or low platelet count	WBCs:	25,500/mcL	Mild anemia
		Segmented neutrophils:	55%	Elevated eosinophils
		Bands:	0%	
		Lymphocytes	6%	
		Monocytes	9%	
		Eosinophils	6%	
		Hemoglobin	13.9 g/dL	
		Platelet count	$212 \times 10^3/\text{mm}^3$	
C reactive protein	Infection/inflammation	0.5 mg/dL	(normal <1.0 mg/dL)	Normal
Coagulation profile	Bleeding disorders	Normal		Normal
Serum chemistry	Electrolytes disturbances	Normal		Normal
Stool microscopy	Infection, inflammation, or parasites	Numerous leucocytes, with 71% eosinophils		Abnormally elevated eosinophils
Stool culture	Infection	Negative for bacteria & viruses		Normal
Stool <i>Clostridium difficile</i>	<i>Clostridium difficile</i> infection	Negative		Normal
Apt test	Maternal swallowed blood	Negative		Normal
Serum total protein	Hypoproteinemia	3.8 g/dL	(normal = 4.4–7.6 g/dL)	Low
Albumin	Hypoalbuminemia	2.0 g/dL	(normal = 3.2–4.8 g/dL)	Low
Serum IgE	IgE-mediated allergic reactions	<1.0 U/mL	(normal = 0.0–6.6 U/mL)	Normal
Blood glucose	Hypoglycemia	Normal		Normal
Liver function tests	Liver disorder	Normal		Normal
Renal function tests	Renal disturbances	Normal		Normal

Abbreviations: CBC = complete blood count; IgE = immunoglobulin E; WBC = white blood cell.

FIGURE 1 ■ A. Upper GI endoscopy view of Baby E with eosinophilic gastroenteritis showing mild inflammatory changes, linear erythema, and flattened duodenal folds. B. Sigmoidoscopic view of Baby E with eosinophilic enterocolitis showing erythema and small aphthous ulcers in the rectosigmoid region.



Upon admission, Baby E was given two normal saline boluses, received nothing per mouth (NPO), and started on D₁₀W, as well as ampicillin and gentamicin for possible sepsis. For the first four days of life, the infant remained NPO on parenteral nutrition. On DOL 5, after the exclusion of all other possible causes of bloody stool and the diagnosis of EG was presumed, feedings with an amino acid milk formula (Neocate 20 kcal/oz.) were started and then changed to a mixed feeding with the amino acid milk

formula and breast milk on DOL 8. Amino acid formula is a hypoallergenic infant formula made of 100 percent individual amino acids with no links to trigger an allergic response. It is specially indicated for the dietary management of CMP allergy, soy milk allergy, and multiple food protein intolerance. The mother was advised to remove all dairy products from her diet several days prior to starting breastfeeding. Baby E remained clinically stable during the entire hospital stay. The bloody stools gradually improved and disappeared

FIGURE 2 ■ A. Colonoscopic view showing normal rectum. B. Sigmoidoscopic view showing normal sigmoid colon.

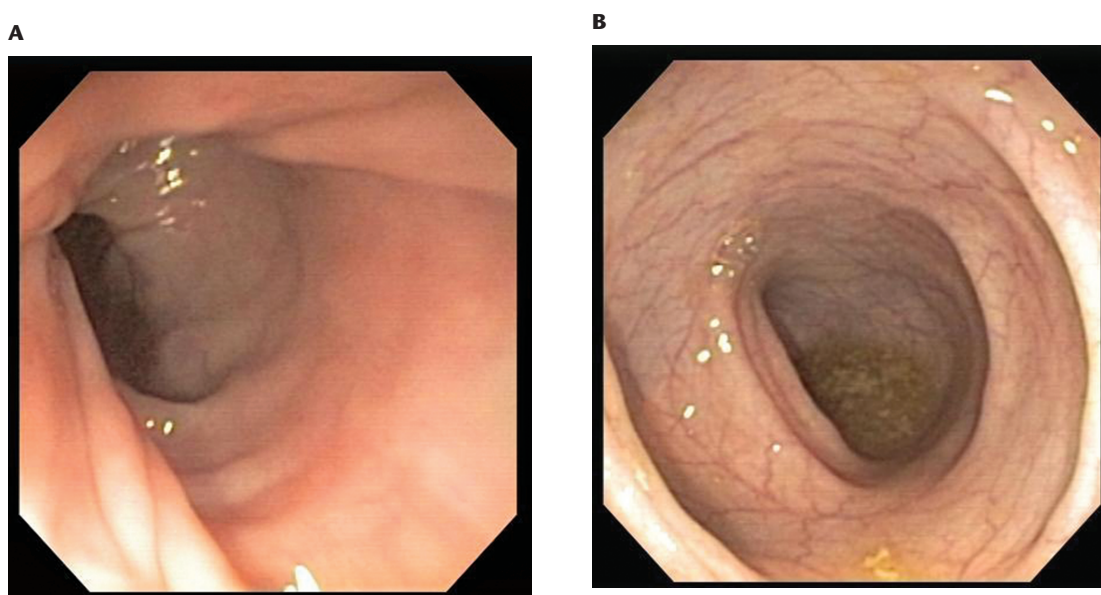
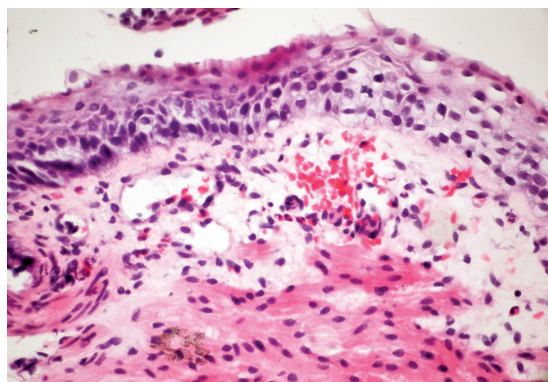
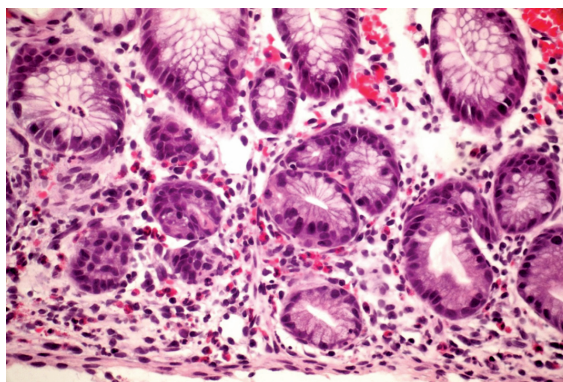


FIGURE 3 ■ Microscopic views demonstrating tissue eosinophilia.

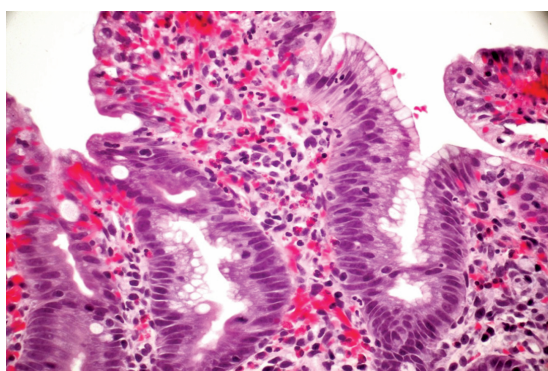
A. Esophagus wall



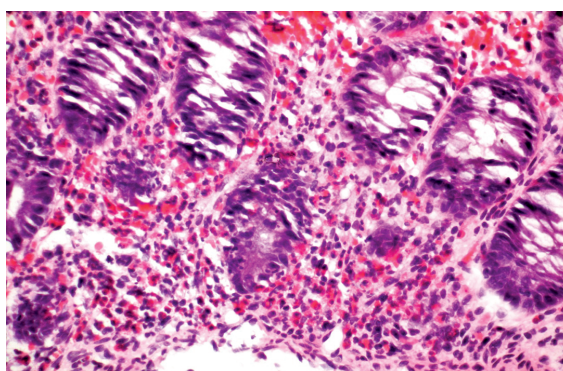
B. Stomach wall



C. Small bowel wall



D. Sigmoid colon wall



by DOL 6. He was discharged home on DOL 11, with no further hematochezia and decreasing peripheral blood eosinophil count. Exclusive breastfeeding continued at home. Rechallenging with CMP formula was not undertaken in this patient because of the severity of the initial GI bleeding at the time of admission. At two months of age, Baby E remained clinically well with normal blood counts, and the parents declined repeat endoscopy.

Although the possibility of intrauterine exposure and sensitization to CMP is still a speculation by some authors,² the diagnosis of EG in our patient was confirmed not only on the

exclusion of other causes of rectal bleeding, but also based on the following findings:

1. Onset of symptoms within few hours after birth prior to initiation of enteral feeding, which suggests that milk protein may be transferred through the placenta
2. The characteristic pathologic features observed in upper and lower GI endoscopy
3. The presence of tissue and peripheral blood eosinophilia
4. The response to elimination of allergens and use of hypoallergenic formula and breast milk after elimination of dairy products from the mom's diet.

TABLE 2 ■ Serial WBCs Showing Peaked Eosinophilia on Day 6 of Life

Finding	DOL 1	DOL 2	DOL 3	DOL 4	DOL 5	DOL 6	DOL 9	DOL 11	DOL 24	DOL 38	DOL 87
WBC ($\times 10^3$)	25.5	29.4	31.7	27.4	31.0	26.4	14.2	12.4	9.0	8.0	7.8
Hgb (g/dL)	13.9	12.6	14.1	12.7	13.5	12.1	11.3	10.3	9.3	9.4	10.4
EO (%)	6.0	15.0	15.0	16.0	17.0	21.0	11.0	5.4	7.0	3.0	2.0
AEC	1530	4410	4760	4390	5270	5540	1640	670	630	240	156

Abbreviations: AEC = absolute eosinophil count; DOL = day of life; EO = eosinophils; Hgb = hemoglobin; WBC = white blood cells.

DISCUSSION

Intrauterine sensitization to CMP has been reported by several authors.^{1,11–14} Szépfalusi et al. reported the presence of cellular proliferation to various allergens in cow's milk (including α -lactalbumin, β -lactoglobulin, casein, α -casein, β -casein, kappa [κ]-casein, and bovine serum albumin) in the cord blood of 39 neonates, which indicates that allergen priming must occur prenatally.¹³ Ward et al. reported a case of fetal sensitization to CMP and wheat, resulting in non-immunoglobulin (IgE) mediated food allergy.¹⁴ Fetal sensitization was indicated by onset of food allergy symptoms shortly after birth and CMP-specific tumor necrosis factor (TNF) production by cord blood mononuclear cells.

Feiterna-Sperling et al. reported a newborn presenting with hemorrhagic meconium in the first hour of life, followed by bloody diarrhea in the next several days.¹¹ On day 14 of life, an elevated total IgE, specific IgE to cow's milk, and an eosinophilia in peripheral blood were found.

Symptoms disappeared when the cow's milk feeding was changed to an extensively hydrolyzed casein-formula. Two challenges with cow's milk formula (on DOL 30 and at seven months of age) were followed by recurrence of vomiting, diarrhea, and failure to thrive. Kumar et al. reported three infants who were fed CMP-based formula and developed rectal bleeding soon after birth, associated with characteristic features of allergic colitis on proctosigmoidoscopy and biopsy.¹ The author presumed that these infants were sensitized to CMP in utero, and the postnatal feeding of these infants with a CMP-based formula was a challenge to these already-sensitized infants. When a casein hydrolysates formula was used for these infants, the inciting antigen (CMP) was removed, leading to resolution of symptoms.

Our EG diagnosis was further supported by the presence of massive GI and peripheral blood eosinophilia, absent of other causes of eosinophilia. The infant's initial and serial CBCs showed increasing eosinophils that peaked on DOL 6, despite being NPO. Eosinophils are WBCs that are mainly involved in control of parasitic infections and allergic diseases such as asthma and food allergy. Tissues of the GI and pulmonary systems are the normal residence for eosinophils, but blood eosinophilia (absolute eosinophil count [AEC] >700 cells/mcL) indicates an eosinophilic disorder.^{15,16} Eosinophils usually constitute <4 percent of the total WBC population,¹⁷ whereas initial eosinophils in Baby E was 6 percent in DOL 1 and peaked to 21 percent in DOL 6. Normally, during the first week of life, AEC is variable, with values ranging from 100 to 2,500 per mm^3 , both in full-term and premature infants.¹⁷ In Baby E, AEC ranged from 1,530 mm^3 in DOL 1 to 5,540 mm^3 in DOL 6. The differential diagnosis of profound peripheral eosinophilia in the neonate is broad, including infectious, immunologic, hematologic, nutritional, and, rarely, malignant etiologies.¹⁸

In addition, histological examination of Baby E's GI biopsy showed abnormal eosinophilic infiltration in the esophagus (5–10 per high power field [hpf]), stomach (>50 /hpf),

duodenum (25/hpf) and sigmoid colon (>50 hpf). The normal number of eosinophils per high power field (eos/hpf) in the GI tract is variable with none in the esophagus, advancing down to the terminal ileum, where more than 30 eos/hpf have been documented.⁴ Although Furuta et al. defined eosinophilic esophagitis by the presence of more than 15 eos/hpf in the esophageal squamous mucosa,¹⁹ there is no such consensus for EG, although most authors have used a diagnostic threshold of 20 eos/hpf.⁵ Tissue eosinophilia in the colon may result from several conditions including parasitic colitis, drug-induced colitis, and allergic colitis. Although EG remains a diagnosis of exclusion, it is possible that CMP antigen sensitization in utero contributed to this condition.

Bone marrow biopsy and aspiration was done for our patient but showed no evidence of clonality or myeloproliferative neoplasm. Rarely, clonal, myeloproliferative, or malignant disorders can present in the neonatal period with marked eosinophilia. Absence of these mutations, normal myeloid:erythroid ratio, and lack of morphologic clonality in the patient's bone marrow made an underlying neoplastic process unlikely.

Rectal bleeding in neonates is an alarming sign that suggests a possible serious underlying condition, leading to hospitalization and thorough evaluation. The presence of blood in stools after birth usually represents benign conditions, but it could be a sign of serious conditions as listed in Table 3.

The most important diagnosis to exclude in the neonate with rectal bleeding is necrotizing enterocolitis (NEC). NEC is mostly seen in a hospitalized preterm infant with small amounts of gross blood in the stool, feeding intolerance, and emerging signs of systemic instability.

Full-term neonates may rarely develop NEC after severe bowel ischemia and early feeding. All sick neonates, particularly premature infants who experience acute hematochezia, should have an abdominal radiograph and a left lateral decubitus radiograph to screen for pneumatosis intestinalis (gas in the bowel, a characteristic radiologic finding in ischemic bowel disease) or free air in the peritoneal cavity. Infectious enterocolitis can present with bloody stool at any age. Enterocolitis in a neonate or infant with abdominal distention and impaired defecation may be caused by Hirschsprung's

TABLE 3 ■ Differential Diagnosis of Rectal Bleeding in Neonates

Benign Conditions	Serious Conditions
Swallowed maternal blood	Necrotizing enterocolitis
Anal fissures	Bacterial enterocolitis
Cow's milk protein allergy	Hirschsprung enterocolitis
	Midgut volvulus
	Intussusception
	Bleeding disorders
	Hemorrhagic disease of the newborn
	von Willebrand disease

disease. Bowel obstruction with ischemic injury should be suspected in an infant with vomiting, pain, and small amounts of blood in the stool. Intestinal volvulus and intussusception are the most important diagnoses. Midgut volvulus refers to twisting of the entire midgut around the axis of the superior mesenteric artery, which can cause severe ischemia and necrosis of the entire midgut—which can be fatal.

Hemorrhagic disease of the newborn is a self-limited bleeding disorder resulting from a deficiency in vitamin K-dependent coagulation factors. Levels of clotting factors II, VII, IX, and X decline rapidly after birth, reaching their nadir at 48–72 hours of life. Hemorrhagic disease of the newborn is a diagnosis that should be considered if the neonate might have failed to receive vitamin K at birth. This is more frequently seen after home births or when vitamin K may not have been administered. Von Willebrand disease is an inherited defect caused by an abnormality, either quantitative or qualitative, of the von Willebrand factor that functions as the carrier protein for factor VIII (FVIII) and is also required for normal platelet adhesion. As such, von Willebrand factor functions in both primary (involving platelet adhesion) and secondary (involving FVIII) hemostasis. Infants with bleeding disorders in addition to bleeding usually have petechial and ecchymotic skin lesions.

Rectal bleeding in otherwise well-appearing infants is often caused by CMP allergy, swallowed maternal blood, or anal fissures. Swallowed maternal blood is particularly suspected if the infant is well appearing and with maternal history of bleeding at birth secondary to placental abruption, placenta previa, or with cesarean section deliveries and fetal vasa previa. The presence of swallowed maternal blood can be easily detected by using the Apt test. Anal fissures produce bright red blood that streaks the stool or causes spots of blood in the diaper. Upon inspection of the anus, a small linear tear will be seen at the anocutaneous junction, most commonly located dorsally in the midline. Rectal bleeding in otherwise well-appearing infants, like Baby E, is most often caused by CMP allergy seen in formula-fed infants, or infants breastfed by mothers who are taking CMP. Symptoms of CMP allergy occur often within the first weeks after the introduction of CMP and can range from mild to moderate to severe.^{20,21} However, many case reports documented its onset within the first 48 hours of life, after introduction of breast or formula milk to those patients.^{1,7,11,22}

CMP allergy, defined as an adverse reaction to one or more proteins of cow's milk, affects 2–3 percent of young children and presents with a wide range of IgE and non-IgE-mediated clinical syndromes.²³ The signs and symptoms of CMP allergy are nonspecific. It can be presented with GI and nutritional, cutaneous, respiratory, and general manifestations. GI manifestations include gastroesophageal reflux, esophagitis, gastritis, delayed gastric emptying, enteropathy, colitis, and constipation. Cutaneous manifestations include urticaria, rash, and swelling of lips or eyelids and pruritus; respiratory manifestations such as runny nose, chronic cough, and wheezing; as well as general manifestations such as food

refusal, failure to thrive, iron-deficient anemia, disturbed sleep, and irritability.^{20,21} No single test is the gold standard for diagnosis, but peripheral blood eosinophilia or eosinophils in the stool are suggestive of eosinophilic colitis. In case of suspected CMP allergy, CMP should be eliminated and replaced by a hydrolyzed protein formula. If the symptoms improve or disappear on an elimination diet, an open challenge with a formula based on whole CMP can be performed two to four weeks after being on hydrolyzed formula under medical supervision. If symptoms of CMP allergy reappear, the suspected diagnosis of CMP allergy is confirmed, and the infant should be maintained on an elimination diet using hydrolyzed formula. Infants who do not develop symptoms on the cow's milk formula during challenge and up to one week after follow-up can resume their normal diet, although they should be monitored.²⁰

CMP allergy is mainly managed by avoiding allergens in infant's formula or the mom's food. For breastfed infants, breastfeeding mothers need to sequentially eliminate all foods that contain CMP including milk, skim milk, buttermilk cream, evaporated or condensed milk, butter, margarine, milk solids, curds, whey, lactose, caseinate, casein, lactalbumin, cheese, yogurt, and sour cream from their diets.²⁴ If an infant remains symptomatic, other protein sources such as soy, egg, and beef may be eliminated as well.^{24,25} The elimination diet should be continued as long as the mother is breastfeeding. When the mother wants to wean her infant, the child should receive an extensively hydrolyzed formula.

For formula-fed infants, either extensively hydrolyzed protein formula or amino acid-based formula (AAF) can be used. Extensively hydrolyzed protein formulas incorporate hydrolysates of casein or whey derived from cow's milk. Their efficacy among those with CMP allergy is approximately 90 percent. AAFs are created from constituent amino acids and have demonstrated efficacy of approximately 99 percent. However, even AAFs contain potentially allergenic material, so their use must be monitored. The taste of the formula might be an issue for compliance; the more hydrolyzed a formula, the worse the taste.²⁴ Although soy protein formulations are cheaper and have a better acceptance than simple amino acid formula, the soy protein is not hypoallergenic, and the risk that the child will develop soy allergy in addition to CMP allergy is high. Also, the use of soy formula in infants younger than six months is discouraged²⁰ because the incidence of soy allergy in soy formula-fed infants is comparable to that of CMP allergy in cow's milk formula-fed babies,^{20,26} and adverse reactions to soy have been reported in 10–35 percent of infants with CMP allergy.²⁷ However, soy protein formula, if tolerated, is an option beyond six months of age. Nutritional counseling and regular monitoring of growth are mandatory in all age groups requiring CMP exclusion.

The overall prognosis of CMP allergy in infancy is good, and most infants will regain tolerance to cow's milk within the first five years of life.²⁸ However, it is reasonable to

reevaluate patients and repeat challenges at regular intervals every six to 12 months in order to assess whether they have developed tolerance to CMP and not to keep them on an elimination diet.²⁸

CONCLUSION

EG is a rare form of CMP allergy. CMP allergies can occur in the early neonatal period, even prior to initiation of enteral feeding, secondary to intrauterine sensitization, and should be considered in the differential diagnosis of any newborn who develops bloody stools. Early diagnosis of the condition and prompt initiation of dietary elimination of CMP are important because both have a great impact on the family and because they need education about early signs and symptoms of CMP allergy and treatment and avoidance strategies. The diagnosis can be made by the healthy appearance of affected infant, the exclusion of other causes of colitis, and the satisfactory response to dietary elimination and treatment with/without the presence of characteristic endoscopic and histopathological findings.

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