

Early Onset Allergic Proctitis in a Preterm Neonate—A Case Report and Review of the Literature

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Abstract

Cow's milk protein allergy/intolerance (CMPA/CMPI) is a common entity in the pediatric population with a nonspecific presentation ranging from gastrointestinal symptoms to systemic manifestations. Most infants with CMPI are term, and symptoms often appear in the week following the introduction of cow's milk-based formula. There is typically a significant delay in the onset of milk allergy in premature infants compared to full term. We report a rare case of a premature neonate who presented with symptoms of CMPA within the first 2 days of life.

Keywords

cow's milk protein intolerance, cow's milk protein allergy, premature infant, intrauterine sensitization

Introduction

Cow's milk protein allergy or intolerance (CMPA/CMPI) is a common entity in the pediatric population, affecting 2% to 5% of formula-fed infants and 0.4% to 0.8% of breastfed infants.¹ Its presentation can be nonspecific, ranging from gastrointestinal symptoms alone to systemic manifestations. Most infants with CMPI are term, and symptoms often appear in the week following the introduction of cow's milk-based formula. A significant delay in the onset of milk allergy in premature infants compared to full-term infants has been reported.^{2,3} CMPI in a premature neonate is relatively rare, and only a few cases have been reported that describe symptoms in the first few days after birth.⁴ We report the case of a premature neonate who presented with symptoms of CMPA within the first 2 days of life.

Case Report

A premature male was born at 33+2 weeks gestational age via urgent Cesarean section due to thick meconium and fetal distress. The pregnancy was uncomplicated. The birth weight was 2350 g. Thick meconium was present at delivery, so he was started on ampicillin and gentamicin pending negative blood cultures. No other indications for sepsis were noted. He was on dextrose

10 % in water (D10W) from birth and was fed expressed breast milk via gavage at 1½ hours of life. The baby's mother adhered to a vegetarian diet but maintained no other dietary restrictions including cow's milk intake. He required supplementation with a commercial cow's milk protein-based formula at 5 hours of life. Streaks of bright red blood were noted in his stool at 32 hours of life. He had been receiving rectal temperatures as part of routine monitoring, which were promptly discontinued. On examination, he had a soft and nondistended abdomen with no palpable hepatosplenomegaly. His anus was patent with no visible fissures. Enteral feedings were

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continued. As for the family history, it was negative for polyps, inflammatory bowel disease, cow's milk protein allergy or other gastrointestinal pathologies, and bleeding diathesis. The parents were nonconsanguineous.

Laboratory testing performed at day 5 showed a red blood cell count of $4.30 \times 10^{12}/L$ (N 4.10–6.70), white blood cell count of $18.3 \times 10^9/L$ (N 9.0–34.0), eosinophil count of $3.20 \times 10^9/L$ (N 0.04–0.80, 15% eosinophils), and normal platelet count ($243 \times 10^9/L$). The baby's coagulation profile (International Normalised Ratio [INR], fibrinogen, prothrombin time and partial thromboplastin time) was normal. These blood-streaked stools persisted multiple times per day in the absence of other clinical symptoms, prompting his transfer to our tertiary care center for further workup on his fifth day of life. General surgery assessed the patient upon his transfer and felt that there was no likely surgical etiology. Abdominal X-ray and ultrasound were grossly unremarkable, except for the incidental finding of left-sided grade 1 hydronephrosis. On day 6 of life, a proctoscopy with rectal biopsy was performed. Grossly erythematous and friable mucosa was noted (Figure 1) and was compatible with proctitis. Rectal biopsy showed a marked increase in intraepithelial eosinophils with eosinophilic abscess formation (Figure 2). Although the crypt architecture was intact, most crypts showed marked increase in intraepithelial eosinophils, increased cellularity of the lamina propria with marked and diffuse eosinophilic infiltrate (85 eosinophils per high-power field [HPF], with a range of 55–85 per HPF), and loss of polarity was noted. More than 60 eosinophils/10 HPF has been used as a diagnostic cutoff for colonic biopsies, while other have suggested 20 eosinophils/HPF. Focal crypt

regenerative changes were noted, and the superficial submucosa showed several eosinophils and an isolated submucosal plexus with ganglion cells. These histological findings were diagnostic of allergic proctitis.

The newborn's formula was changed to an amino acid-based formula, and breast feeding was discontinued. Within 2 days, the blood-streaked stools had ceased. At the 3-month follow-up, the baby continued to feed amino acid-based formula and had no gastrointestinal symptoms. Cow's milk challenge was introduced after a 10-month period, and on follow-up, he was symptom free and showed a weight of 10.09 kg (86%, $Z=1.08$), a length of 69.1 cm (7%, $Z=-1.45$), and a weight-for-height is at 99th percentile ($Z=2.41$). There was no concern with his growth. During the 3 years from the initial presentation, there was no recurrence of symptoms.

Discussion

CMPA results from sensitization to β -lactoglobulin in cow's milk. Although CMPA is increasingly documented in the neonatal period,^{5,6} CMPA presenting in the first 48 hours is rare in term infants and extremely rare in premature infants (Table 1). To our knowledge, this is only the second CMPA reported in a premature infant that presented within 48 hours of life. We have compared our case to 4 other documented cases of CMPA diagnosed in both term and preterm infants presenting with bloody stools in the absence of systemic features within the first 48 hours of life (Table 1).^{5,7}

CMPA can be a manifestation of IgE-mediated and non-IgE-mediated pathways. IgE-mediated pathway results in an immediate allergic reaction including symptoms such as urticaria, rash, wheeze, or cough, and non-IgE-mediated pathway results in a more complex, delayed response, usually within the first 4 weeks of life or later.^{1,8} Isolated blood-streaked stool is characteristic of non-IgE-mediated CMPA and is referred to as allergic proctitis or allergic proctocolitis.^{6,9} CM-induced enterocolitis presenting in the first week of life has been cited in some case reports and surveys in term and preterm newborns.^{5,7,10–12} In some cases, the symptoms start prior to any oral intake.^{10–12} This early form of allergic enterocolitis suggests intrauterine sensitization due to either CM antigen present in the amniotic fluid¹⁰ or antigen crossing the placenta⁸ to elicit an allergic response in the fetus. The extremely early onset of symptoms in our case suggests an intrauterine sensitization to cow's milk protein via maternal diet. The presence of meconium, which likely indicates in utero fetal distress, may also suggest intrauterine sensitization. Meconium passage is rare before 34 weeks of gestation.¹³

Gastrointestinal symptoms in neonates often cause concern for a serious underlying pathology, especially when infants are preterm. Underlying etiologies for

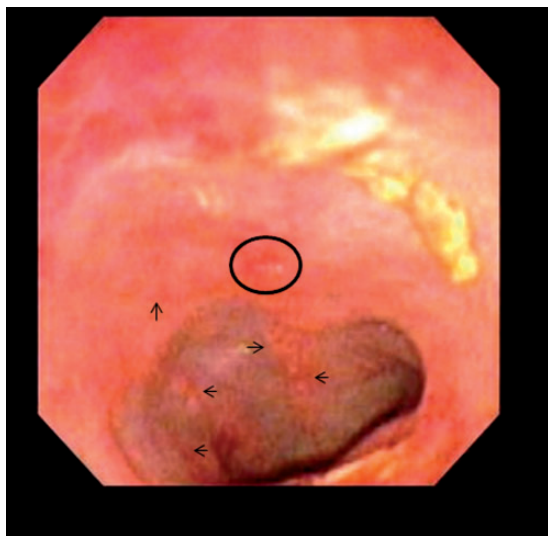


Figure 1. Proctoscopy showing erythematous (arrow head) and focally eroded mucosa (arrow).

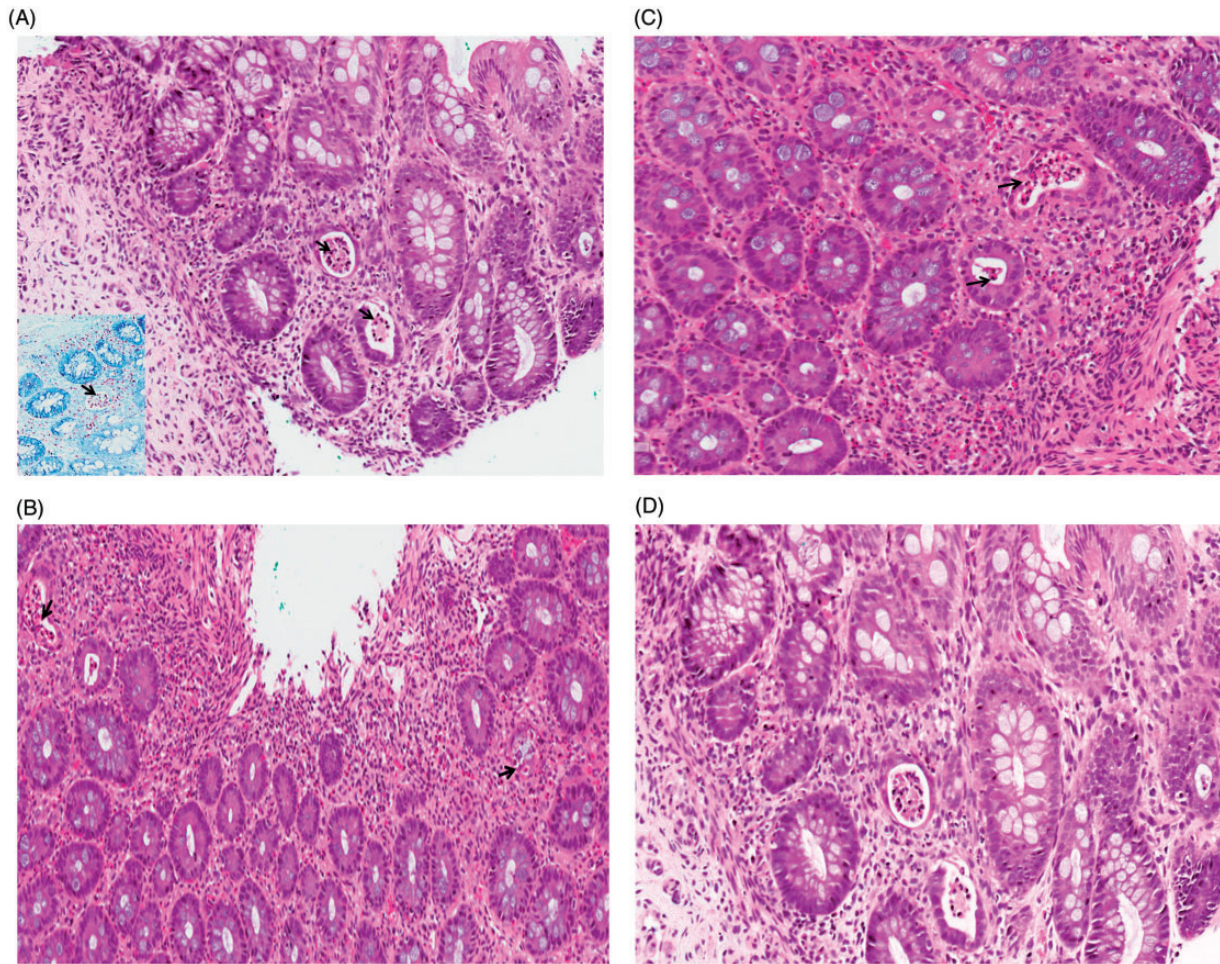


Figure 2. A–D, Medium- and high-power views of the rectal mucosa with diffuse and marked increase in eosinophils. Note the arrows marking crypt luminal eosinophilic abscesses and that eosinophilic infiltrate extends to the muscularis mucosa. D, Giemsa stain highlighting eosinophils is shown. hematoxylin phloxine saffron (HPS) $\times 200$ and $\times 400$.

bloody stools frequently include necrotizing enterocolitis, sepsis, or bleeding diathesis. In many cases, a thorough history and physical examination successfully rule out these conditions, and these neonates are frequently managed conservatively.

In an otherwise well neonate presenting with rectal bleeding without anal fissures, differentials include idiopathic neonatal transient eosinophilic colitis (INTC) and food-protein-induced proctocolitis.¹⁴ Drug-induced colitis could also be considered but was an unlikely etiology in our case because there was no history of drug use and no generalized pathology beyond colorectal involvement. The most common drugs that can lead to colitis are non-steroidal anti-inflammatory drugs, rifampicin, clozapine, tacrolimus, and gold, which are usually used in a setting of organ transplants or autoimmune diseases. Diagnosis of non-IgE-mediated CMPA is made definitively by double-blinded placebo-controlled food challenge.^{1,15} However, due to the risk of severe allergic reaction or significant symptomatology following the procedure,

this food challenge is not standard of care. The histological findings including eosinophilic infiltration in our patient were markedly beyond what normally could be expected and fit emerging diagnostic criteria for CMPA.^{16–18} However, reliance on suggestive biopsy results and response to allergen elimination may still result in the overdiagnosis of CMPA in infants with INTC.^{11,19} Controlled oral food challenges remain the gold standard in the diagnosis of food-related symptoms, especially if performed in a double-blinded, placebo-controlled manner.

Management following a diagnosis of CMPA involves the avoidance of the allergen. In breastfed infants, mothers should avoid all dietary sources of milk products for up to 2 weeks before expecting to see improvement in neonatal symptoms.^{15,20} In formula-fed infants, options for management include an elimination diet with extensively hydrolyzed infant formulas (efficacy of 90%)²¹ or amino acid-based formulas (efficacy of 99%). In either case, resolution of symptoms is typically seen within 48 to

Table 1. Comparison of Reported Patient Demographics.

Demographics	Preterm (This Study)	Preterm (Faber et al. ⁵)	Term Case No. 1 (Kumar et al. ⁷)	Term Case No. 2 (Kumar et al. ⁷)	Term Case No. 3 (Kumar et al. ⁷)
Birth weight (kg)	2.35	2.57	3.8	3.3	4.0
Gestational age	Preterm 33+2 weeks	Preterm 33 weeks	Term	Term	Term
Gender	Male	Male	Female	Male	Male
Race	Egyptian	Unknown	African American	African American	African American
Maternal parity	G2	Unknown	Unknown	Unknown	Unknown
Maternal age	39 Years	Unknown	23 Years	36 Years	17 Years
Maternal infection	No	Unknown	Unknown	Unknown	Unknown
Maternal diet	Vegetarian	++Milk daily	Unknown	Unknown	Unknown
Consanguinity	No	No	Unknown	Unknown	Unknown
Age of first feeding (h)	1.5	2	1	0.8	0.7
Diet before symptoms	EBM/CMPF	CMPF	CMPF	CMPF	EBM/CMPF
Onset of hematochezia (h)	32.5	4	28	25	27
Infant well?	Yes	Yes	Yes	Yes	Yes
Interim management	Continued PO feeds	NPO IV antibiotics Stool culture	NPO IV antibiotics Stool culture	NPO IV antibiotics Stool culture	NPO Stool culture
Gross imaging colonoscopy	Erythematous and friable mucosa in patches	Unknown	Friable, edematous colonic mucosa	Bloody, friable colonic mucosa, ulcers rectum	Eosinophilia, edema, hemorrhage
Eosinophilia biopsy (HPF)	85	130/10	Seen, not quantified	>60/10	Seen, not quantified
Serum IgE (IU/ml)	Unknown	Unknown	<1	Unknown	<2
Absolute eosinophil count (mm ³)	3.20 × 10 ⁹ /L (N 0.04–0.80)	Unknown	712	Unknown	720
Feed after diagnosis	AAF	AAF	EHF	EHF	EHF
Family history of CMPI	No	Yes	No	Unknown	Unknown
Family history of atopy	Unknown	Unknown	Yes	Unknown	Yes
Follow-up	At 3 months, AAF	Unknown	At 12 months, EHF	At 17 months, unrestricted diet	At 4.5 months, EHF

Abbreviations: AAF, amino acid-based formula; CMPF, cow milk protein formula; EBM, expressed breast milk; EHF, extensively hydrolyzed formula; HPF, high-power field; IV, intravenous (intravenous therapy); NPO, not per oral (withhold oral intake of food and fluids).

72 hours after the initiation of a cow's milk protein-free diet.¹⁰ Timing of the oral food challenge in this population is suggested between 9 and 12 months.^{1,22}

Conclusion

In contrast to previous reports, early onset of rectal bleeding due to an allergic proctitis can occur within hours after birth in a premature infant. To our knowledge, this is the second case description of a premature infant with rectal blood loss due to CMPA within the first

hours after birth. CMPA is an increasingly common entity not only in term but also in premature neonates. Diagnosis of non-IgE-mediated CMPA can be approached differently in otherwise healthy premature infants compared to those experiencing systemic manifestations of the condition.

Declaration of conflicting interests

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