รายงานผู้ป่วย (Case Report)

ภาวะลำไส้เน่าอักเสบกลับเป็นซ้ำในทารกเกิดก่อนกำหนดที่แพ้โปรตีนนมวัว: รายงานผู้ป่วย

เบญจารัตน์ ทรรทรานนท์ (พ.บ.)[1] ศุภมาศ ศุภบรรพต (พ.บ.)[1] และ สุภารัตน์ จีวรตานนท์ (พ.บ.)[2]

[1]ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยบูรพา จังหวัดชลบุรี ประเทศไทย
[2]กลุ่มงานกุมารเวชกรรม โรงพยาบาลชลบุรี จังหวัดชลบุรี ประเทศไทย

บทคัดย่อ

บทนำ ภาวะลำไส้เน่าอักเสบเป็นภาวะฉุกเฉินทางระบบทางเดินอาหารพบบ่อยในทารกคลอดก่อนกำหนด การแพ้โปรตีนนมวัวอาจแสดงอาการเลียนแบบหรืออาจเพิ่มความเสี่ยงต่อการบาดเจ็บของลำไส้ กรณีศึกษานี้ยังพบไม่บ่อยนัก

วัตถุประสงค์ นำเสนอกรณีทารกคลอดก่อนกำหนดที่มีภาวะลำไส้เน่าอักเสบกลับเป็นซ้ำ โดยมีภาวะแพ้โปรตีนนมวัวเป็นปัจจัยร่วมที่น่าสงสัย

รายงานผู้ป่วย ทารกเพศหญิงอายุครรภ์ 34 สัปดาห์ น้ำหนักแรกเกิด 2,030 กรัม ถ่ายเป็นเลือดตอนแรกเกิด 2 ชั่วโมง ได้รับการรักษาด้วยการงดนม ให้สารน้ำและยาปฏิชีวนะ กลับมาถ่ายปกติตอนอายุ 2 วัน ตอนอายุ 9 วัน มีถ่ายเป็นเลือดและมีอุณหภูมิกายต่ำ เม็ดเลือดขาวในเลือดสูง เลือดเป็นกรดและโปรตีนในเลือดต่ำ ภาพรังสีสอดคล้องกับภาวะลำไส้เน่าอักเสบระยะ IIB จึงงดนมและให้ยาปฏิชีวนะอีกครั้ง จากนั้นให้นมแม่ร่วมกับนมสูตรสำหรับทารกก่อนกำหนด ตอนอายุ 27 วันหลังได้รับนมต่อเนื่อง 8 วัน มีอาการถ่ายเป็นเลือดซ้ำ ท้องอืด การเคลื่อนไหวของลำไส้ลดลง ผลเพาะเชื้อเลือด ปัสสาวะ อุจจาระ และน้ำไขสันหลังไม่พบเชื้อ ได้รับการรักษาด้วยงดนมและยาปฏิชีวนะ นึกถึงภาวะลำไส้เน่าอักเสบกลับเป็นซ้ำจากภาวะแพ้โปรตีนนมวัวร่วมด้วยหลังจากให้นมแม่ที่งดผลิตภัณฑ์นมร่วมกับนมสูตรโปรตีนผ่านการย่อยเต็มที่ อาการทางคลินิกและภาพรังสีดีขึ้นอย่างชัดเจนและไม่มีภาวะลำไส้เน่าอักเสบซ้ำอีก

สรุป กรณีศึกษานี้สะท้อนถึงความท้าทายในการจำแนกภาวะลำไส้เน่าอักเสบออกจากภาวะแพ้โปรตีนนมวัวในทารกคลอดก่อนกำหนด โดยภาวะแพ้โปรตีนนมวัวอาจเลียนแบบหรือเป็นปัจจัยเสี่ยงให้เกิดภาวะลำไส้เน่าอักเสบ การนึกถึงภาวะแพ้โปรตีนนมวัวในทารกที่มีภาวะลำไส้เน่าอักเสบซ้ำ จึงมีความสำคัญช่วยให้จัดการการรักษาได้อย่างเหมาะสม

คำสำคัญ ภาวะลำไส้เน่าอักเสบ ภาวะแพ้โปรตีนนมวัว ทารกคลอดก่อนกำหนด

ผู้นิพนธ์ที่รับผิดชอบ เบญจารัตน์ ทรรทรานนท์
ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยบูรพา
จังหวัดชลบุรี ประเทศไทย
E-mail: benzjarut@hotmail.com

Cow's milk protein allergy presenting as recurrent necrotizing enterocolitis in preterm neonates: A Case Report

Benjarat Dardaranonda (M.D.)[1] Supamas Supabanpot (M.D.)[1] and Suparat Chivaratanond (M.D.)[2]

[1]Department of Pediatrics, Faculty of Medicine, Burapha University, Chonburi, Thailand
[2]Department of Pediatrics, Chonburi Hospital, Chonburi, Thailand

Abstract

Introduction: Necrotizing enterocolitis (NEC) is a major cause of morbidity in preterm infants. Cow's milk protein allergy (CMPA) may mimic NEC or predispose to intestinal injury, but recurrent NEC associated with CMPA is rarely reported.

Objective: This study reviewed recurrent NEC in a preterm female infant born at gestational age (GA) 34 weeks presented with recurrent bloody stools at day of life (DOL) 27 despite prior recovery from the first NEC stage IIB on DOL 9. Given the temporal relationship with cow's milk protein exposure and subsequent clinical improvement with cow's milk protein elimination, CMPA was strongly suspected as a contributing factor.

Case presentation: A preterm female infant born at GA 34 weeks, birth weight 2030 g, with no perinatal complications was presented with grossly bloody stools on DOL 1 and empiric antibiotics were initiated. On DOL 9, the infant developed hypothermia and recurrent bloody stools. Laboratory tests revealed leukocytosis and metabolic acidosis, while abdominal radiographs demonstrated pneumatosis intestinalis and portal venous gas, consistent with NEC stage IIB. Management included bowel rest, and broad-spectrum antibiotics. Feeding was reintroduced with breast milk plus preterm formula after being kept nil per os (NPO) for 10 days. Feedings were advanced after NPO for 10 days. At DOL 27, after advanced with breast milk plus preterm formula for 8 days, the infant developed recurrent bloody stools despite prior recovery. Stool cultures were negative, and abdominal examination revealed marked distension with hypoactive bowel sounds. Recurrent NEC was diagnosed. After NPO 10 days and broad-spectrum antibiotics. Feeding with breast milk that maternal eliminated diary product and extensive hydrolysate formula was reintroduced until full feed. After change of formula promptly showed resolution of symptoms with improved radiological findings. Given the temporal relationship with cow's milk protein exposure and subsequent clinical improvement with cow's milk protein elimination, CMPA was strongly suspected as a contributing factor.

Conclusion: This case highlights the complex interplay between NEC and CMPA. CMPA should be considered in preterm infants, our case most likely represents CMPA as a predisposing condition that increased intestinal vulnerability to true NEC episodes.

Keywords: Necrotizing enterocolitis (NEC), Cow's milk protein allergy (CMPA), Preterm infants

Corresponding author: Benjarat Dardaranonda
Department of Pediatrics, Faculty of Medicine,
Burapha University, Chonburi, Thailand
E-mail: benzjarut@hotmail.com

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Introduction

Necrotizing enterocolitis (NEC) is a major cause of morbidity in preterm infants. Cow's milk protein allergy (CMPA) may mimic NEC or predispose to intestinal injury, but recurrent NEC associated with CMPA is rarely reported.

A broad range of allergic disorders and intolerances are associated with cow's milk protein in the infant diet. CMPA and intolerance are well recognized in otherwise healthy term infants, with prevalence in challenge-confirmed studies free from selection bias ranging from 1.9% to 4.9 %[1]. These disorders can be classified according to their immunopathogenesis as IgE-mediated, non-IgE-mediated, or T-cell–mediated. The clinical spectrum is broad, ranging from mild gastrointestinal symptoms to severe sepsis-like presentations such as food protein–induced enterocolitis syndrome (FPIES)[2], while food protein–induced enteropathy (FPE) typically presents with chronic diarrhea[3]. Food protein-induced intolerance in the otherwise healthy infant stands in contrast to enterocolitis that typically occurs in the preterm neonate.

Bloody stools in a preterm infant are most concerning for NEC, the most common gastrointestinal emergency in the neonatal intensive care unit (NICU) and a leading cause of neonatal morbidity and mortality[4]. In the United States, the incidence of NEC is estimated at 1-3 per 1,000 live births, rising to 5-7% in the very low birth weight population[5,6]. In Thailand, the incidence of NEC is 2.8 cases per 1,000 live births occurred with a mortality rate of 27.3%.[7]

NEC is considered a multifactorial disease, with proposed mechanisms including immaturity of the gut barrier, dysbiosis, intestinal ischemia, and enteral feeding. Its primary triggers include exposure to formula (cow's milk protein), hypoxia, hemodynamic compromise, and uncontrolled inflammatory responses in the premature intestine.[8]

Distinguishing NEC from CMPA can be clinically challenging in preterm infants, as both may present with rectal bleeding and feeding intolerance. Late preterm infants with colitis often have both NEC and CMPA on the differential diagnosis. In some cases, recurrent or mild NEC-like episodes may in fact reflect an underlying food protein intolerance. By contrast, in term and near-term infants, CMPA is the most common cause of rectal bleeding, with a more favorable prognosis and very low risk of mortality. CMPA has been described both as a mimicker of NEC and as a potential predisposing factor, possibly through mucosal injury and aberrant immune responses. Recurrent NEC episodes in preterm infants, therefore, raise the possibility of an underlying allergic component.[9]

We report a preterm infant who developed recurrent NEC-like illness with temporal association to cow's milk protein exposure, highlighting the need to consider CMPA in such cases.

Objective

This study reviewed recurrent NEC in a preterm female infant born at GA 34 weeks presented with recurrent bloody stools at day of life 27 despite prior recovery from the first NEC stage IIB at DOL 9. Given the temporal relationship with cow's milk protein exposure and subsequent clinical improvement with cow's milk protein elimination, CMPA was strongly suspected as a contributing factor.

Methods

The record of one patient was reviewed, and relevant clinical data was collected. A review of the literature about CMPA, NEC, and CMPA presenting as recurrent NEC in preterm neonates was made. The data for this retrospective descriptive study was gathered from the inpatient and outpatient medical records at Burapha University Hospital between May 2024 and June 2025. The Research Ethics Committee of Burapha University, Chonburi, Thailand, approved this study (HS024/2568).

Case presentation

A preterm female infant born at GA 34 weeks to an 18-year-old primigravida via normal vaginal delivery. Birth weight was 2030 g (appropriate for gestational age), and Apgar scores were 9, 10, 10 at 1, 5, and 10 minutes, respectively. Maternal history was notable for teenage pregnancy and late antenatal care; maternal serology was negative. The infant developed grossly bloody stools on DOL 1, approximately two hours after birth and prior to the initiation of breastfeeding. Comprehensive physical examination revealed no evidence of neonatal sepsis or intestinal obstruction. She was kept NPO, underwent gastric lavage with 40 mL of normal saline until the aspirate was clear, and serial hematocrit monitoring was initiated. The differential diagnoses considered included swallowed maternal blood, NEC, coagulopathy, neonatal sepsis, and CMPA. Initial laboratory results on DOL 1 are summarized in Table 1. The complete blood count demonstrated marked eosinophilia (24%) without leukocytosis, anemia, or thrombocytopenia. Empiric therapy with ampicillin and gentamicin was initiated after septic workup.

After being kept NPO for 24 hours, the hematochezia resolved. Enteral feeding with breast milk plus preterm formula was initiated on DOL 2. Empirical antibiotics were discontinued after 72 hours when blood cultures showed no growth.

Table 1 Complete blood count panel at DOL1 and DOL9

Serum	Patient value		Reference range and units[10]
	DOL1	DOL9	
WBC	21,760	43,580	9,100-34,000/mm^3
Neutrophil	38	44	%
Lymphocyte	29	33	%
Monocyte	7	14	%
Eosinophil	24	6	%
Band	0	2	
Hemoglobin	13.4 g	13.4 g	15-24.0/dL
Hematocrit	42	43	40-70%
Platelet count	336×10^3	305×10^3	150-400×10^3 cells/mL

After stepwise advancement of enteral feeding with breast milk plus preterm formula, the infant achieved full feeds. On DOL 9, at a postmenstrual age (PMA) of 35 weeks, she developed hypothermia and recurrent bloody stools. She was able to receive enteral feeding at a reduced milk volume, and there was no vomiting. Physical examination revealed a firmly distended but non-tense abdomen, with sluggish bowel sounds and no evidence of lethargy. Additional laboratory investigations were performed to evaluate the cause of her symptoms. The complete blood count demonstrated leukocytosis (Table 1). The C-reactive protein was 1.36 mg/L(<5mg/L). Blood chemistry revealed metabolic acidosis (Bicarbonate 8 mmol/L) (22-29 mmol/L) and hypoalbuminemia (2.4 g/dL) (2.5-3.4 g/dL). Stool examination was positive for occult blood. Abdominal radiographs demonstrated pneumatosis intestinalis and portal venous gas as shown in Figure 1A, B. A diagnosis of NEC, stage IIB, was established. The infant was managed medically as definitive NEC with intravenous antibiotics (cefotaxime, amikacin, and metronidazole), gastrointestinal decompression and parenteral nutrition. Clinical improvement was noted over the next day with negative blood, urine, stool, and cerebrospinal fluid cultures. Enteral feeding was resumed with breast milk plus preterm formula following the NPO period.

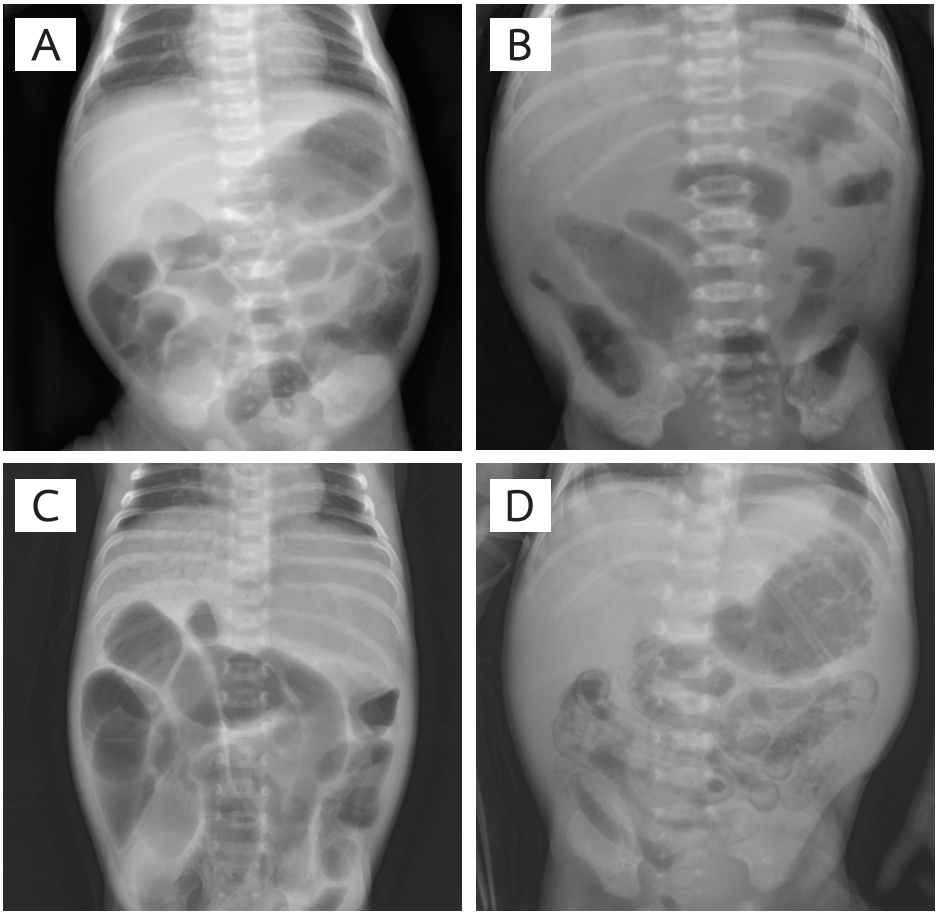

Figure 1 (A) Supine abdominal X-ray showing nonspecific diffuse bowel dilatation with foci of pneumatosis (left lower quadrant) upon presentation on DOL 9. (B) Diffuse dilatation of bowels with foci of portal vein gas (right upper quadrant) at 6 h after presentation on DOL 9. (C, D) Recurrent pneumatosis and portal vein gas on DOL 27

Seven days after resuming enteral feeds with breast milk plus preterm formula (DOL 27, PMA 37+6wk), the infant developed diffuse abdominal distension, and hypoactive bowel sounds with grossly bloody stools. The abdominal X-ray showed diffuse pneumatosis with portal vein gas (Figure 1C, D). She had a third sepsis workup, was made NPO and monitored for clinical progression of the disease. The infant was managed medically as definitive NEC with intravenous antibiotics (Cefotaxime, Amikacin, and metronidazole), gastrointestinal decompression and parenteral nutrition again. A repeat sepsis evaluation and stool cultures for bacteria and virus were all negative. She was observed for clinical and radiological signs over the next several days.

After resolution of this episode, feeding with breast milk that maternal eliminated diary product and extensive hydrolysate formula was reintroduced until full feed. After change of formula promptly showed resolution of symptoms with improved radiological findings.

This 34-week premature infant developed three clinical episodes of allergic enterocolitis mimicking NEC with definitive pneumatosis and portal vein gas on abdominal X-ray each time. The recovery was complete with conservative management and without progression of the illness with recurrence of clinical signs and symptoms related to milk protein exposure each time. This infant was discharged on breast milk that maternal eliminated diary product and extensive hydrolysate formula. At 12 months visit the baby is growing well without any intolerance to feeds.

The suspicion of CMPA arose after the second episode of NEC when symptoms recurred soon after reintroduction of cow's milk based formula, while cultures for enteric pathogens remained negative. The infant subsequently improved after switching to an extensively hydrolyzed formula, with no further recurrence of bloody stools or abdominal distension. This clear temporal relationship between cow's milk protein exposure and relapse, followed by improvement after elimination, supported CMPA as an underlying contributor.

The episode of DOL 9 met criteria for NEC stage IIB, with pneumatosis intestinalis and portal venous gas., findings not typical of allergic enterocolitis alone. However, the recurrence of NEC-like illness at DOL 27 in the absence of sepsis or other precipitating factors, together with the temporal association with cow's milk protein exposure and subsequent clinical improvement after dietary elimination, suggests that CMPA may have been a pre-existing condition that increased the risk of NEC recurrence rather than a simple mimicker. Therefore, our case most likely represents CMPA as a predisposing condition that increased intestinal vulnerability to true NEC episodes.

Recurrent NEC versus CMPA was considered. The temporal relationship with cow's milk protein exposure and subsequent clinical improvement with elimination suggested CMPA as the underlying etiology

Discussion

Cow's milk protein allergy (CMPA) is the most common food allergy in infants, but its presentation as enterocolitis in preterm neonates is rarely reported. Our patient developed hematochezia within hours of birth and later experienced recurrent NEC-like episodes with eosinophilia and radiographic findings, all resolving after removal of cow's milk protein. This case highlights the diagnostic challenge of differentiating NEC from CMPA in preterm infants and emphasizes the need to consider CMPA when NEC recurs or presents atypically. A preterm infant may be first diagnosed with suspected NEC then subsequently diagnosed with CMPA with improvement of symptoms after treating NEC.[11,12]

The three essential components for the development of NEC are injury to the bowel mucosa, presence of bacteria and availability of metabolic substrate.[13,14] This

clinical course suggests that events related to severe gastrointestinal injury and onset of NEC could be involved in the pathogenesis of CMPA in preterm Infants[15].

Several clinical features may help differentiate CMPA from NEC in preterm infants. CMPA generally occurs after repeated exposure to cow's milk proteins, while NEC typically presents earlier in the feeding course. Infants with NEC often exhibit systemic instability, including metabolic acidosis, temperature dysregulation, and lethargy, whereas CMPA tends to cause localized gastrointestinal manifestations such as hematochezia or feeding intolerance without significant systemic illness. Radiographic findings such as pneumatosis intestinalis and portal venous gas are characteristic of NEC but are rarely observed in isolated CMPA. Laboratory abnormalities, including marked leukocytosis, elevated C-reactive protein, and thrombocytopenia, are more pronounced in NEC. In contrast, CMPA usually demonstrates mild or absent inflammatory responses. Importantly, a clear temporal relationship between cow's milk protein exposure and symptom recurrence, followed by rapid improvement after elimination of cow's milk-based feeds, strongly favors a diagnosis of CMPA or overlapping disease.

Conclusions

This case highlights the complex interplay between NEC and CMPA. Given the similar presentation of CMPA and NEC in preterm infants, it is possible CMPA may be misdiagnosed as NEC. CMPA should be considered in preterm infants. Clinical overlap in the symptoms and pathophysiology of CMPA and NEC in preterm infants. Both entities are marked by proceeding gut dysbiosis and dysregulation of the adaptive immune systems.

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