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Case Report

Cow milk protein allergy presenting as feeding intolerance and eosinophilia: case reports of three preterm neonates

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Three preterm infants with cow milk protein allergy (CMPA) presented with feeding intolerance, sepsis-like episodes and persistent moderate-to-severe eosinophilia. After eliminating cow milk, the clinical symptoms improved significantly. CMPA can cause common manifestations in sick preterm infants such as feeding intolerance and eosinophilia.

Keywords: Cow milk protein allergy, Preterm infant, Feeding intolerance, Eosinophilia

Introduction

Cow milk protein allergy (CMPA) is the most common food hypersensitivity in infants. The diagnosis is difficult in preterm infants because their clinical symptoms can mimic common symptoms in sick neonates such as abdominal distension, bloody stools and symptoms of necrotising enterocolitis (NEC).^{1–3} Eosinophilia is common in sick preterm and term newborns, with the incidence ranging from 14% to 76%.⁴ There are few reports of preterm infants with CMPA and eosinophilia. Three preterm infants are described.

Case 1

A male preterm infant was born to a 35-year-old Thai mother at 33 weeks gestation with a birthweight of 980 g (<3th percentile). He was treated for respiratory distress with conventional mechanical ventilation for 3 days. Premature formula was commenced on day 2. On day 3, he developed feeding intolerance with bilious and bloody gastric residuals (incomplete digested food retained in the stomach) and constipation. The abdomen was distended with decreased bowel sound.

Investigations. Haemoglobin (Hb) was 16.7 g/dl, white cell count (WCC) $6.03 \times 10^9/L$, neutrophils $2.41 \times 10^9/L$ ($1.1–9.0 \times 10^9/L$), eosinophils $0.44 \times 10^9/L$ ($0–0.7 \times 10^9/L$) and platelets $1.21 \times 10^9/L$. C-reactive protein (CRP) was 2.57 nmol/L (<4.76). Sepsis work-up including stool for occult blood, blood and CSF cultures were negative. An abdominal radiograph demonstrated marked dilation of the stomach with normal bowel gas pattern. The infant was treated as probable NEC, feeds were stopped for 3 days and he was given empirical antibiotics for 7 days. Enteral feeds were recommenced with premature formula which resulted in recurrence of increased gastric residuals and poor weight gain. The eosinophil count increased to $9.64 \times 10^9/L$ (day 26) (Fig. 1). The mother had a history of allergic rhinitis and a high daily consumption of cow milk (2000 ml/day) during pregnancy. The infant's serum-specific IgE (sIgE) to cow milk was 7.77 kUA/L (<0.1). He was diagnosed as CMPA and feeds were changed to a casein hydrolysed formula (Pregestimil®, Mead Johnson, New Jersey, USA). His clinical symptoms continued to improve with good weight-gain and the eosinophil count decreased to $2.22 \times 10^9/L$ (day 31) (Fig. 1). One week after the elimination diet, cow milk was re-introduced for 4 days, which resulted in recurrence of increased gastric residuals and abdominal distension, and a rise in the eosinophil count to $16.59 \times 10^9/L$ (day 38). Consequently, the diagnosis of CMPA was confirmed. The feed was changed back to Pregestimil®, the symptoms of cow milk intolerance gradually improved and by day 60 eosinophils had decreased to $0.9 \times 10^9/L$. He was discharged on day 67 weighing 2000 g (<3th percentile).

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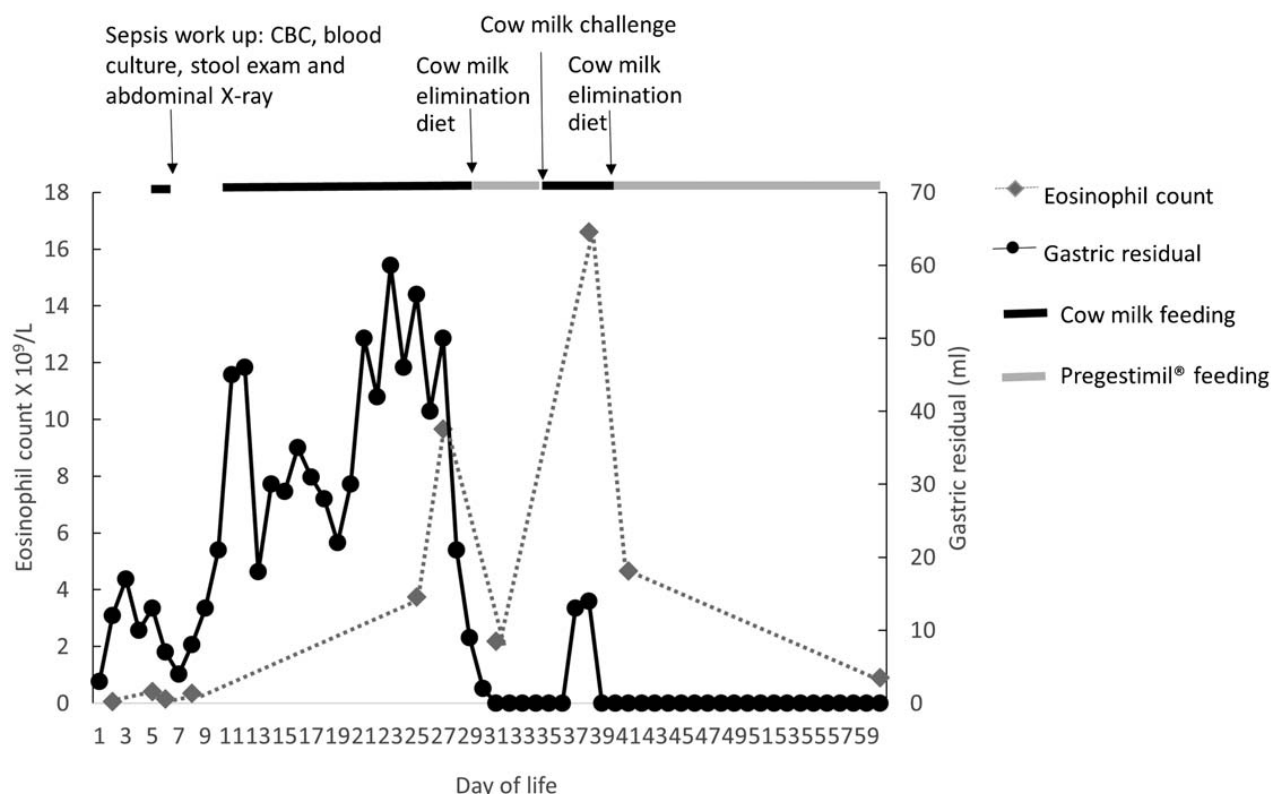


Figure 1 Case 1: The association between the eosinophil counts, amount of gastric residuals and exposure to cow milk or extensively casein hydrolysed formula during hospitalisation

At 1 year of age, his sIgE to cow milk had decreased significantly to 0.30 kUA/L. However, after cow milk challenge at home, he developed a maculo-papular rash and itching. A cow milk elimination diet was advised and to re-challenge with cow milk in 6–12 months.

Cases 2 and 3

Two preterm female monozygotic twins were born to a 26-year-old Thai mother at 27 weeks gestation. During pregnancy, the mother consumed an increased amount of cow milk as food supplementation for the twins and she had a history of allergic rhinitis. The infants were delivered by caesarean section and weighed 1070 g (50th–90th percentile) (A) and 1050 g (50th–90th percentile) (B). Their respiratory distress was treated for 4 days with surfactant and nasal continuous positive airway pressure.

Twin A was fed with preterm formula on day 3. On day 10, she developed feeding intolerance and abdominal distension with a normal stool pattern.

Investigations. Hb was 15.5 g/dl, WBCs $15 \times 10^9/L$, neutrophils $2.81 \times 10^9/L$, eosinophils $0.39 \times 10^9/L$, platelets $214 \times 10^9/L$ and CRP 2.83 nmol/L. Sepsis work-up including stools for occult blood, blood and CSF culture were negative. Abdominal radiograph demonstrated a decreased bowel gas pattern. The infant was treated as early sepsis, feeds were stopped for 2 days and she received intravenous antibiotics for 7 days. Feeds of premature formula were resumed and were

well tolerated for 6 days. On day 19, she developed diffuse abdominal distension with bilious gastric residuals. Investigations demonstrated a neutrophil count of $5.44 \times 10^9/L$, and the eosinophil count had risen to $2.72 \times 10^9/L$ and CRP was 2.57 nmol/L. A sepsis work-up similar to that of the previous episode was negative. Feeds were stopped for 1 day and she was given intravenous antibiotics for 4 days which brought clinical improvement. Three days after recommencing feeds of preterm formula (day 23), she developed a third episode of feed intolerance, frequent apnoea, oxygen desaturation and abdominal distension with normal bowel movements. The neutrophil count was $2.76 \times 10^9/L$, eosinophils $1.68 \times 10^9/L$ and CRP 2.29 nmol/L. Abdominal radiograph demonstrated generalised bowel dilation. Sepsis work-up (same as in previous episode) was negative. Her serum IgE to cow milk was 0.39 kUA/L. She was diagnosed as CMPA and the feeds were changed to Pregestimil®. Ten days later, her eosinophil count had decreased from 1.68 to $0.81 \times 10^9/L$ (Fig. 2). She was discharged on day 62 weighing 2180 g (3rd–10th percentile). She continues to be followed up and remains well with good weight gain.

The second twin (B) was fed with preterm formula on day 2. On day 10, she developed feed intolerance and abdominal distension. Investigations showed a normal white blood cell count with neutrophils $6.35 \times 10^9/L$, eosinophils $0.15 \times 10^9/L$ and CRP 4.10 nmol/L. Abdominal radiograph showed a decreased

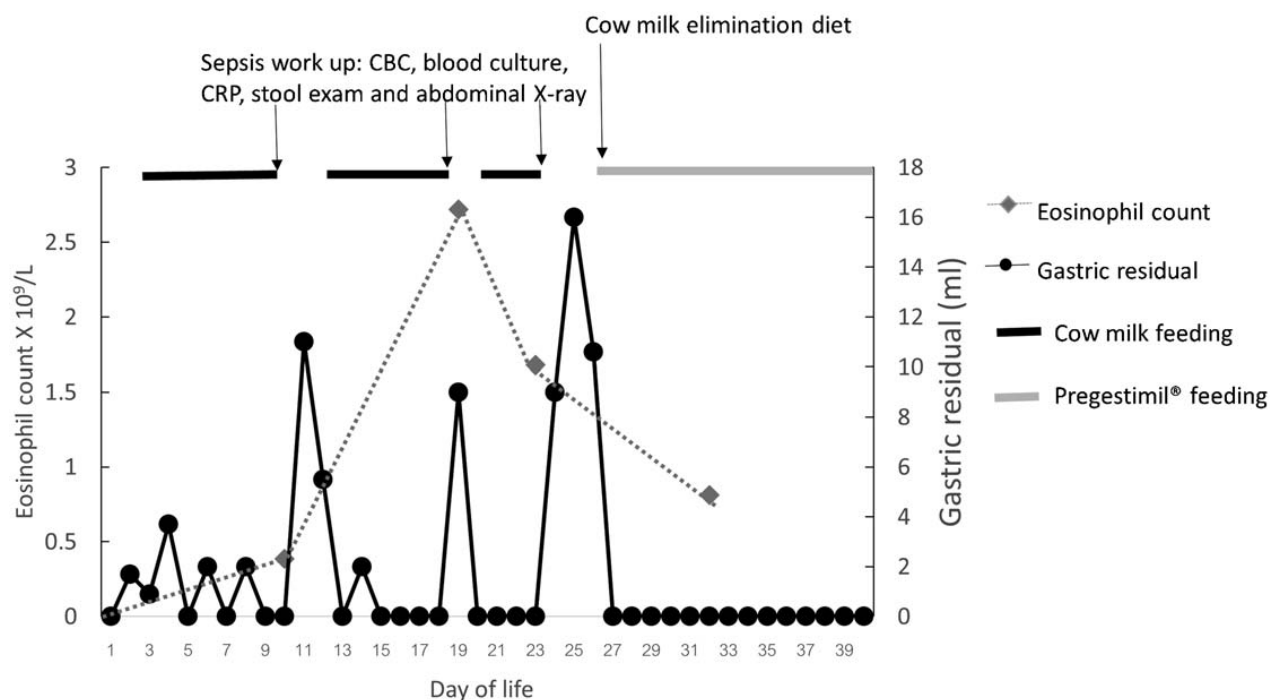


Figure 2 Case 2: The association between the eosinophil counts, amount of gastric residuals and exposure to cow milk or extensively casein hydrolysed formula during hospitalisation

bowel gas pattern. Feeds were stopped for 2 days and she received intravenous antibiotics for 7 days. Sepsis work-up including blood and CSF culture and stool examination for occult blood were all negative. Feeds of preterm formula were resumed but 7 days later (day 20), she developed frequent apnoea, oxygen desaturation and diffuse abdominal distension but with normal bowel movements. Investigation demonstrated a normal white blood cell count with neutrophils $4.32 \times 10^9/L$, but the eosinophil count had risen from 0.15 to $2.01 \times 10^9/L$, and CRP was 3.05 nmol/L. sIgE to cow milk was 0.23 kAU/L. Repeat sepsis work-up was negative. Because her clinical symptoms resembled those of her twin, CMPA was suspected. Enteral feeds of Pregestimil® were recommenced. Fourteen days after cow milk elimination, her eosinophil had decreased from 2.01 to $0.52 \times 10^9/L$ (Fig. 3). She was discharged on day 62 weighing 2050 g (3rd percentile). She continues to be followed up and remains well with good weight gain.

The clinical symptoms and investigations in these three infants are summarised in Table 1.

Discussion

The three preterm infants presented with feed intolerance, sepsis-like episodes and moderate-to-severe eosinophilia. In the first case, CMPA was diagnosed by recovery from symptoms after eliminating cow milk, a positive sIgE to cow milk and a cow milk challenge test. The second and third cases had similar clinical symptoms with moderate eosinophilia and slightly increased sIgE to cow milk. They were diagnosed with CMPA on the basis of recovery from

symptoms after eliminating cow milk and evidence of sIgE positivity for cow milk.

CMPA is the most common food intolerance in infants and young children. However, its prevalence in preterm infants is not known. A survey using questionnaires in Japan demonstrated a 0.21% prevalence of CMPA in neonates including preterm and full-term infants.² Symptoms of CMPA commonly involve the gastro-intestinal tract (GI), respiratory system and skin. In preterm infants, GI presenting symptoms can be non-specific, e.g. feed intolerance, gastro-oesophageal reflux-like disease and lower gastro-intestinal bleeding which may be clinically indistinguishable from early NEC.^{6,7} Allergic reaction to cow milk can be classified as immediate (typically IgE-mediated) and late-onset (non-IgE-mediated and mixed IgE- and cell-mediated) reactions.⁸ Immediate reactions can present as systemic reactions (anaphylaxis), cutaneous and/or respiratory symptoms which occur within minutes after ingesting cow milk. Late-onset reactions occur hours to several days after ingesting cow milk and GI symptoms are common in neonates and infants.⁹ Specific IgE or skin prick test to cow milk are useful in diagnosing IgE-mediated intolerance, but results might be negative if symptoms are non-IgE-mediated.¹⁰ However, a recent study in Japan has shown positive specific IgE to food in 30% of cases of infants with gastro-intestinal food allergy.⁹ This is consistent with these three infants in whom IgE to cow milk was highly positive in the first case and slightly positive in the second and third cases. This emphasises the difference in gastro-intestinal food allergies between Asian

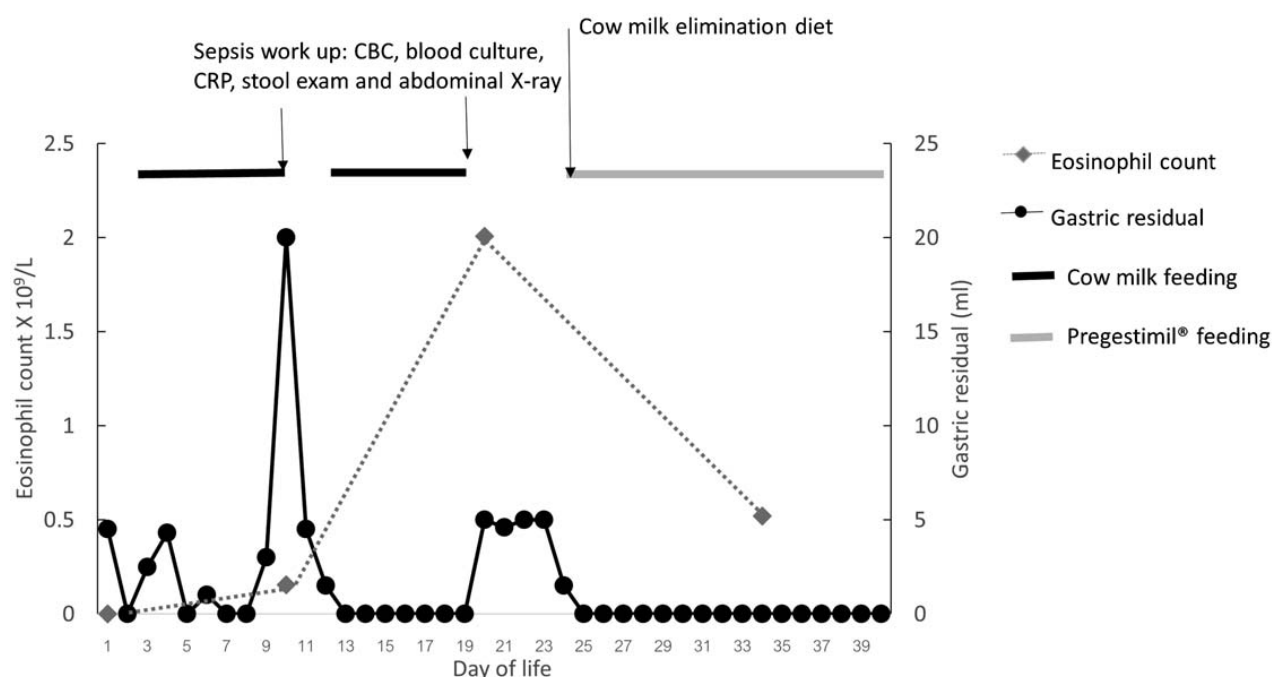


Figure 3 Case 3: The association between the eosinophil counts, amount of gastric residuals and exposure to cow milk or extensively casein hydrolysed formula during hospitalisation

and Western populations: the latter normally test negative for food-specific IgE.⁹

The oral food challenge is considered to be the gold standard for diagnosing CMPA. However, cow milk challenge was only undertaken in the first case, resulting in recurrence of symptoms similar to the presenting ones, i.e. feed intolerance and severe eosinophilia. Cow milk challenge was not undertaken in the second and third cases because their parents refused consent. Therefore, the diagnosis of CMPA in the two latter cases relies solely on the clinical improvement after eliminating cow milk. Further cow milk challenge may be needed to confirm the diagnosis.

Eosinophilia in neonates is defined as an eosinophil count of $>0.7 \times 10^9/L$ and has been subclassified as mild ($0.7\text{--}0.99 \times 10^9/L$), moderate ($1.0\text{--}2.99 \times 10^9/L$) or severe ($>3.0 \times 10^9/L$).¹¹ Eosinophilia is common in hospitalised preterm infants and infection and NEC are the major causes. However, the majority have only mild eosinophilia.¹¹ Eosinophilia as a major

presentation of CMPA in neonates is uncommon. Nonetheless, eosinophilia has also been proposed to be a marker of atopy in infants.¹²

Reports of the association between eosinophilia and CMPA in preterm infants are limited. Reports from Italy and the USA have described preterm infants presenting with recurrent typical NEC episodes with eosinophilia and the symptoms improved after eliminating cow milk.^{3,7} A recent report from Japan described a preterm infant who presented with bloody stool, persistent acidemia and severe eosinophilia.¹ In contrast with previous reports, our cases did not have typical clinical symptoms of NEC or bloody stools. All three developed feed intolerance and abdominal distension which were indistinguishable from an episode of sepsis. All investigations for sepsis were negative including blood culture and CRP. The only prominent abnormal investigation was persistent eosinophilia. From the evidence of these cases and previous reports, the clinical manifestations of CMPA in preterm infants can be the common clinical

Table 1 Summary of patients' data

	Case 1	Case 2	Case 3
Gestational age, wk	33	27	27
Birthweight, g	980 (<3rd percentile)	1070 (50–90th percentile)	1050 (50–90th percentile)
Clinical symptoms			
Bilious gastric residuals	Yes	Yes	No
Bloody gastric residuals	Yes	No	No
Abdominal distension	Yes	Yes	Yes
Ileus	Yes	Yes	Yes
Apnoea	No	Yes	Yes
Maximum eosinophil count, $\times 10^9/L$	16.59	2.72	2.01
Serum IgE to cow milk, kUA/L	7.77	0.39	0.23
Total IgE, IU/ml	114.3	4.0	<2

symptoms of sick preterm infants including feed intolerance, bloody stools, abdominal distension, sepsis and NEC-like episodes. CMPA should be suspected if these clinical symptoms persist, associated with moderate-to-severe eosinophilia.

It has been proposed that the mechanism of development of CMPA is an imbalance between immunological tolerance and sensitisation (IgE production) resulting in clinical manifestation of cow milk allergy. It has been proposed that several factors including genetic background, dose of cow milk, frequency of administration, age at first cow milk exposure, immunological status of the host and cow milk transmission via breast-milk affect the CMPA immunological mechanism.¹⁰ In these case reports, the infants' mothers had underlying allergic diseases and histories of ingestion of increased amounts of cow milk during pregnancy. Early exposure to cow milk and sensitisation *in utero* in conjunction with immaturity of the mucosal barrier of the GI tract may result in increased uptake of cow milk antigen, leading to the development of CMPA soon after birth.

Treatment of CMPA includes avoidance of cow milk protein and replacing it with an appropriate formula to fulfil infants' nutritional requirements. Guidelines for managing CMPA have recommended the use of extensively hydrolysed, amino acid-based formulae in infants with GI manifestations.^{10,13}

This report highlights that feed intolerance and sepsis like-episodes, the common presenting symptoms of hospitalised preterm infants, can be caused by CMPA, especially when it occurs with persistent moderate-to-severe eosinophilia. Early detection and

a proper elimination diet will promote appropriate growth in preterm infants.

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