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Case Report

Pneumatosis intestinalis: Does it always indicate necrotizing enterocolitis?

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ABSTRACT

Background. Pneumatosis intestinalis (PI) is a rare radiological finding that may be associated with various diseases. In the neonatal period, it is considered pathognomonic for necrotizing enterocolitis (NEC). Cow's milk protein allergy (CMA) is the main cause of allergy especially in term infants appearing following breastfeeding or consumption of milk-based formulas.

Case Report. We report three neonates presenting with PI and diagnosed with CMA and/or NEC. Case 1 was a 44-day-old preterm infant admitted to the hospital for nutritional deficiency and jaundice, who later developed PI and a NEC-like appearance (NEC-LA). Case 2 was born at 28 weeks' gestation and developed PI and NEC-LA five times. Case 3 was a 24-day-old term neonate who was admitted to the hospital due to acute gastroenteritis and developed PI and NEC-LA. Only case three required a surgical intervention. After feeding the infants an amino acid-based formula, clinical manifestations improved quickly, and the disease did not relapse. In our opinion, CMA was the correct diagnosis for cases 1 and 3. However, case 2 developed two NEC episodes and three NEC-LA episodes, which were thought to be related to CMA.

Conclusions. In addition to NEC, CMA should be considered in every PI, and recurrent NEC feeding should begin in accordance with a CMA management protocol.

Key words: cow's milk protein allergy, necrotizing enterocolitis, neonate, pneumatosis intestinalis.

Pneumatosis intestinalis (PI), is a rare form of air leak into the gastric and intestinal wall and often is used as the radiological finding in preterm infants to diagnose necrotizing enterocolitis (NEC).[1-3] The pathogenesis of PI is still unknown. It may occur due to inflammation, infection, ischemia, trauma, or autoimmune processes.[2] Although the etiology and clinical course are various, physicians tend to treat all PI similarly. Bowel rest, broad-spectrum antibiotics, and hemodynamic support are the basis of the treatment.[4,5] If PI is not related to NEC, enteral nutrition can be initiated early, and a prolonged course of broad-spectrum antibiotics is not recommended.[1]

The most common food allergy of infancy is cow's milk protein allergy (CMA) which is an immune-mediated hypersensitivity response to some proteins in cow's milk.[6] The immunological response can be IgE-mediated, non-IgE-mediated, or mixed and the clinical presentation depends on the type of the immunological response including cutaneous, gastrointestinal, respiratory, and systemic symptoms.[6,7] The diagnosis is based on history and physical

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examination. In exclusively breastfed infants, the mothers should be put on a cow's milk-free diet. In non-exclusively breastfed infants, a formula with reduced allergenicity for cow milk protein is recommended.[7]

Herein, we report three neonates presenting with PI with different etiologies mimicking NEC. Informed consent were obtained from the families.

Case presentations

Patient 1

A 44-day-old male baby was referred to our hospital due to nutritional deficiency and jaundice. His gestational age (GA) and birth weight (BW) were 32 weeks and 1810 g, respectively. According to the medical reports of the previous hospital, he was hospitalized in the neonatal intensive care unit (NICU) for 35 days where he received total parenteral nutrition (TPN) for three weeks as he could not tolerate breast milk or formula and was diagnosed with sepsis caused by *Serratia marcescens*. On presentation to our hospital, his weight was 2120 g (<3rd percentile), and height was 47.5 cm (10-50th percentile). Physical examination revealed umbilical hernia, and icterus. Laboratory data on admission showed conjugated hyperbilirubinemia. The infant was hospitalized in our pediatric ward for the regulation of nutrition and further investigations. Upon receiving preterm formula, he developed feeding intolerance, abdominal distention and emesis. On day of life (DOL) 55 and 56, abdominal X-ray (AXR) showed gas distension and PI (Fig. 1 A for DOL 55 and B for DOL 56). Abdominal ultrasound (AUS) demonstrated air in the intestinal wall and portal system. He was diagnosed with NEC and transferred to the NICU. Feeding was stopped, and intravenous antibiotics were initiated after the sepsis workup. C-reactive protein (CRP) was 49.9 mg/dL and fecal occult blood test was positive. He was electively intubated and placed on mechanical ventilation (MV) to reduce intraluminal pressure in the intestines and was put on gastric decompression, which relieved his abdominal distension, and the next day he was extubated. The complete blood count showed 28.9% eosinophilia and cow's milk specific IgE was positive (0.83 kU/L). Blood culture was negative. He received antibiotics for 14 days and enteral feeding was resumed with an amino acid-based formula (AABF) on DOL 70. After feeding with formula, his clinical condition remained well. The infant was discharged on AABF on DOL 84 with the diagnosis of NEC and CMA.

Patient 2

A male preterm baby with a BW of 765 g was born at 28 GA via Cesarean section due to preeclampsia. The baby was put on noninvasive MV, received prophylactic antibiotics and TPN plus trophic feeds were started with breast milk. In the first DOL the baby developed abdominal distention and an AXR was remarkable for gas distension in the bowel loops. Considering NEC, enteral feeding was discontinued. Abdominal distention regressed on DOL 5, the infant was extubated, and enteral feeding was started and increased gradually. On DOL 9, 31, 60 and 85 the infant developed vomiting and abdominal distention. Laboratory findings were within the normal range apart from elevated CRP. Fecal occult blood test was positive in every episode. AXR demonstrated PI (Fig. 1C for DOL 31-Fig. 1D for DOL 60-Fig. 1E for DOL 85). AUS confirmed NEC (Fig. 2). We additionally detected a left femoral fracture on DOL 68 (Fig. 1F) caused by metabolic bone disease of prematurity. In every episode, enteral feeding was discontinued, fluid and broad-spectrum antibiotic treatments were initiated after cultures were obtained and he was intubated to alleviate abdominal distention. Blood cultures revealed no growth, so antibiotics were given for 7-10 days, and we suspected the patient had CMA and began feeding him exclusively with AABF. The mother was put on a milk-free diet and after three days breastfeeding was resumed. However, due to the mother's non-

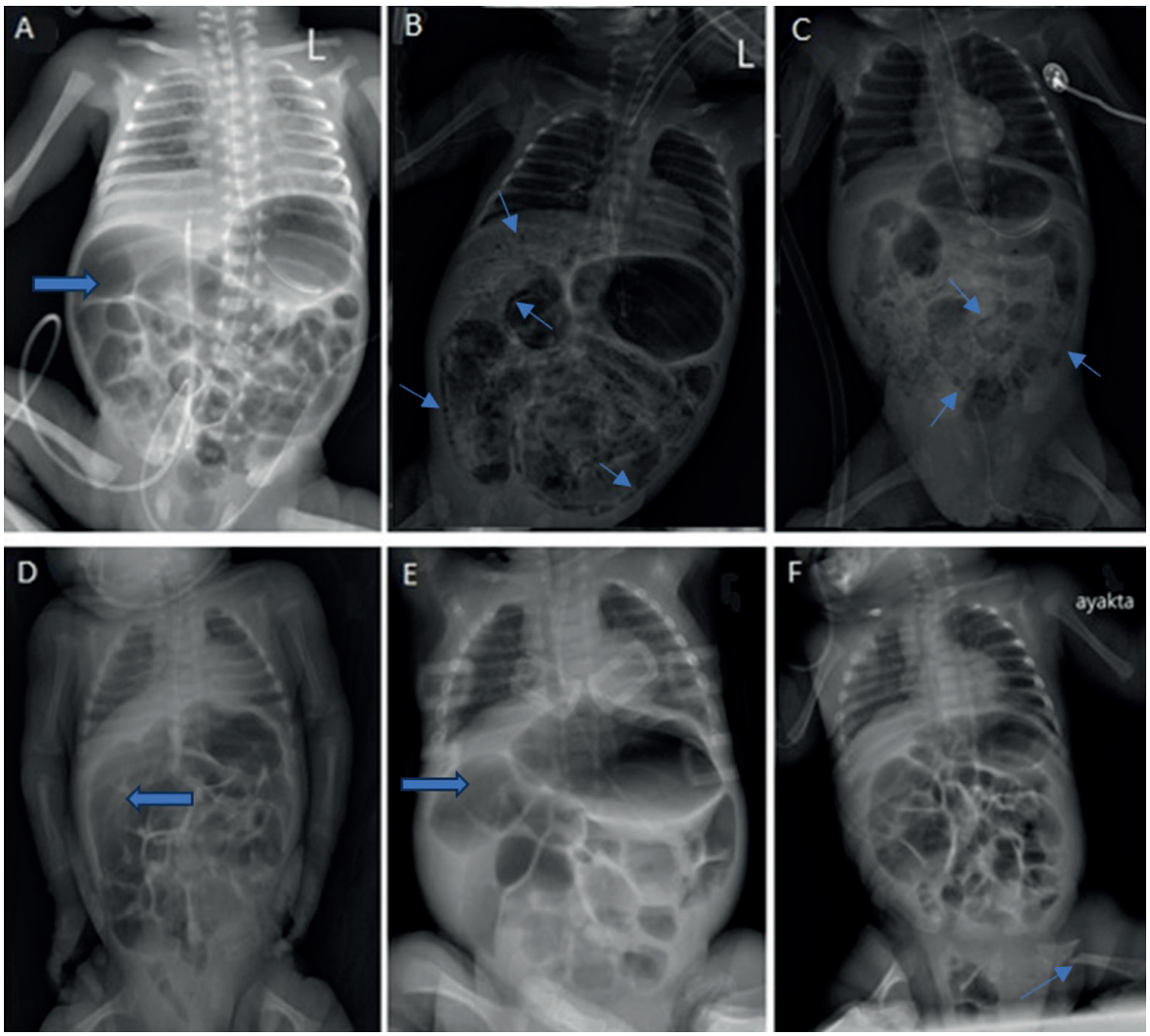

Fig. 1. A, B: Gas distension in bowel loops (thick arrow), pneumatosis intestinalis including the entire intestines and in the portal vein (thin arrows). C, D, E: Distension with gas was observed in the bowel loops (thick arrows). There were also linear and circular air lucencies in the bowel wall (thin arrows). F: Fracture in the left femur (thin arrow).

compliance with the diet, the baby experienced two additional episodes. We insisted that the mother follow a strict elimination diet. There were no further attacks after the fifth, but on DOL 152, an upper gastrointestinal tract endoscopy was performed due to a refusal of breastfeeding, which revealed esophagitis, esophagus, and gastric motility disorders. He was diagnosed with both NEC and CMA. On DOL 154, the infant was discharged on AABF and breast milk.

Patient 3

A 24-day-old baby boy was admitted to our NICU after two days of diarrhea with mucoid stools, vomiting, and fever. The baby, born at full term (39 weeks of gestation), was the first child of the 24-year-old mother and was delivered via Cesarean section. His parents reported that due to maternal lactation insufficiency, formula feeding began on DOL 10. His physical examination revealed mild

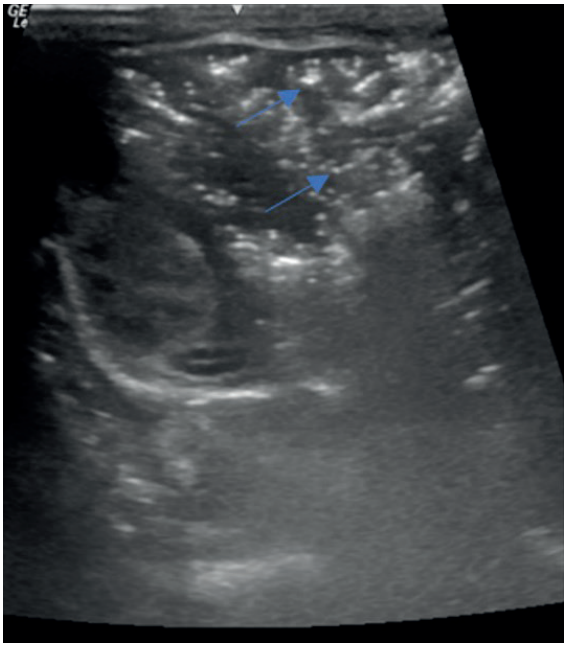

Fig. 2. Ultrasonography revealed intense air echoes in the intestinal wall and portal system (blue arrows).

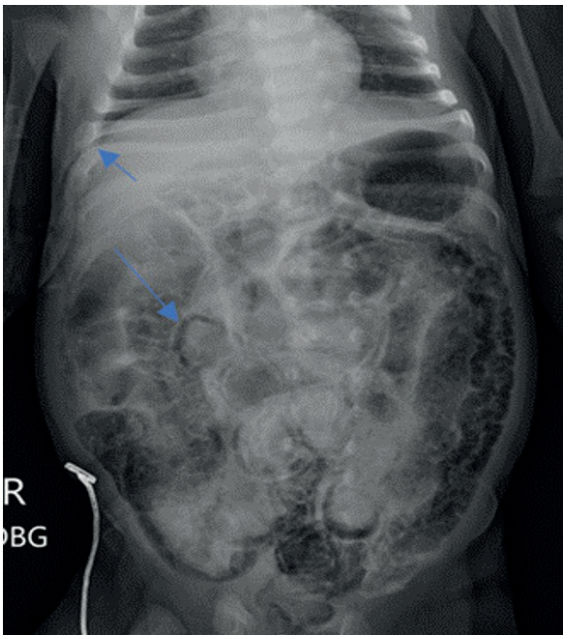

Fig. 3. Pneumatosis intestinalis (long arrow) and suspicious air lucency superposed on the lateral section of the liver (short arrow).

abdominal distention and cutis marmorata. Blood tests revealed elevated CRP levels (44 mg/dL), while stool tests for viral antigens and stool analysis were negative. Ampicillin sulbactam and gentamicin were initially given. Fluid therapy and enteral feeding were initiated. On DOL 27, the infant experienced severe abdominal distention and bloody stools. CRP was 187 mg/dL, and procalcitonin was above 100 ng/mL. AXR revealed suspicious air lucency superimposed on the lateral section of the liver and PI (Fig. 3), which was confirmed by AUS. Due to the possibility of perforation, exploration was performed, but no bowel perforation was found (Fig. 4). Enteral feeding was stopped, and TPN was initiated. The blood, peritoneal, and intraoperative abdominal free fluid cultures remained sterile, and antibiotic treatment was discontinued on DOL 37. The infant was diagnosed with CMA after suffering from acute gastroenteritis, and feeding was initiated with AABF and on DOL 45, the infant was discharged solely on AABF.

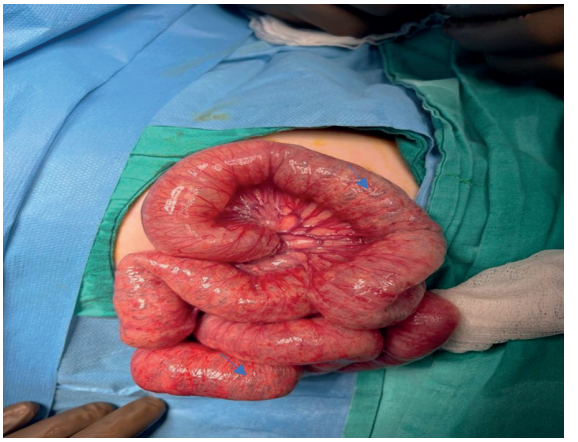

Fig. 4. During exploration, pneumatosis intestinalis (blue arrows) was observed throughout the entire small intestine, starting 75 cm distal to the Treitz ligament and extending to 5 cm from the cecum, involving all intestinal walls. The circulation, wall color and structure of the stomach appeared satisfactory. The liver and gallbladder were normal in appearance.

Discussion

In this paper, we described the clinical, laboratory, and radiological courses of three neonates with PI detected on AXR.[5,8] PI can be idiopathic or due to a benign condition (primary - 15%) or due to an unclear etiology or NEC (secondary - 85%).[8] It is often associated with NEC in the neonatal period. However, other rare conditions can also cause PI. Lenfestey et al.[9] reviewed 56 infants diagnosed with NEC. Of the 56 infants, five had an atypical course and were diagnosed with food protein-induced enterocolitis. Kalra et al.[10] reported a preterm infant who developed PI due to isolated ruptured appendicitis on DOL 13. Deutsch et al.[11] reported a 20-day-old neonate who was a victim of child abuse and presented with PI. A 30-day-old preterm infant presented with acute abdominal distension and PI, which was later diagnosed with meconium inspissation.[12] Capitanio et al.[13] reported PI in two infants with rotavirus gastroenteritis. Despite the wide range of conditions that can cause PI, it is critical to distinguish NEC from non-NEC causes because treatments differ. As suggested in the literature, upon detecting abdominal distension and PI, regardless of the cause, we stopped enteral feeding, intubated the babies to relieve abdominal distension, and initiated broad-spectrum antibiotics.[1]

NEC is a multifactorial acute inflammatory bowel necrosis affecting 10% of very low birth weight infants, resulting in death and morbidity.[3,14] As GA decreases, the onset of NEC occurs later.[15] Despite the nonspecific clinical, laboratory and radiographic findings, the mainstay of the diagnosis is AXR. AXR and AUS can show portal venous gas (PVG), PI, or pneumoperitoneum.[3,16] The initial management is supportive including bowel rest, hemodynamic support, and broad-spectrum antibiotics. In addition, to reduce gastrointestinal luminal pressure, elective intubation and ventilation, switching from noninvasive to invasive ventilation mode and gastric decompression are recommended.[1] In infants with bowel perforation, surgical resection of the necrotic bowel may be necessary.[2,17]

Cow's milk protein allergy is a benign condition that typically arises after the introduction of breast milk or milk-based formula. The exact mechanism is not clear. Most of the neonates diagnosed with CMA are term and it is mostly non-IgE-mediated. The infants may have cutaneous, gastrointestinal, respiratory, and systemic symptoms including atopic eczema, poor feeding, irritability, failure to thrive, abdominal pain, colic, vomiting, rectal bleeding and bloody or mucoid stools.[18] Infants with skin manifestations are more likely to have specific IgE positivity than infants with gastrointestinal manifestations.[7] The diagnosis of CMA and NEC in the early stage is a challenge due to similar radiologic findings including intestinal dilatation, PI and PVG. Guo et al.[19] reported that during the follow-up, intestinal motility outside the pathological area was different, and the duration of PVG was shorter in CMA, which could help distinguish CMA from NEC. To confirm the diagnosis of CMA, the CM protein must be eliminated for 1-4 weeks and then challenged or reintroduced orally.[7,18] Mothers who are exclusively breastfeeding should refrain from consuming milk and milk products while continuing to breastfeed. Non-breastfed infants should receive AABF.[6,7,18]

It is worth noting that, preterm CMA may mimic NEC and may be misdiagnosed as NEC. Furthermore, CMA was reported as a pre-existing condition that increases the risk of NEC or vice versa.[18] Despite the unknown association between NEC and CMA, it was postulated that after intestinal inflammation and mucosal damage plus atrophy, the infant becomes more vulnerable to CMA due to increased intestinal permeability.[20] As suggested in the literature, before making a definitive diagnosis, we primarily diagnosed our patients with NEC. Although case 1 was initially diagnosed as NEC, we changed the final diagnosis to CMA due to the late onset of symptoms, eosinophilia, and cow's milk specific IgE positivity. Case 2

developed five clinical episodes of enterocolitis, the first and second of which were caused by NEC, but the others were believed to be caused by CMA. Previous studies have shown that NEC causes intestinal damage and facilitates the development of CMA; additionally, CMA may predispose to the development of NEC.[18,20] Case 3 was exclusively fed CM protein-based formula, developed gastroenteritis on DOL 24, and was the only infant who required surgery for a suspected perforation. However, no surgical pathology was detected, and he was diagnosed with CMA. It was reported that PI may be associated with gastroenteritis, so we believed that the infant had CMA following gastroenteritis.[13]

In conclusion, the presence of PI on AXR is frequently regarded as a diagnostic marker for NEC. However, other conditions, such as CMA or gastroenteritis, may produce the same radiological findings. CMA is rare in neonates, and the findings may coincide with NEC. The correlation of history, physical examination, laboratory, and radiological findings is critical for accurate diagnosis and management. The significance of these three cases stems from the recognition that NEC and CMA can be developed concurrently, sequentially, or in similar ways. As a result, CMA should be considered in every PI, and if an infant develops recurrent NEC, feeding should begin in accordance with a CMA management protocol.

Ethical approval

Since this is a retrospective case report, we only obtained consent from the families. Written informed consent was obtained from parents of the patients.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: YC,TG,ÇA; data collection and literature review: YC, MAÖ; interpretation of results: YC, KK, draft manuscript preparation;MAÖ. Critically review of the manuscript: TG, ÇA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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