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Early onset Food Protein–Induced Enterocolitis Syndrome in two breastfed newborns masquerading as surgical diseases: case reports and literature review

Luca Bosa¹, Stefano Martellosi², Giacomo Tardini¹, Paola Midrio³, Paola Lago⁴

1 Department of Woman's and Child's Health, University of Padova, Padova, Italy

2 Pediatric Unit, Ca' Foncello Hospital, Treviso, Italy

3 Pediatric Surgery Unit, Ca' Foncello Hospital, Treviso, Italy

4 Neonatal Intensive Care Unit, Ca' Foncello Hospital, Treviso, Italy

Corresponding author:

Luca Bosa, MD

E-mail: lucabosamd@gmail.com

Telephone number: +393470482503

Personal postal address: Via San Francesco 177, 35121 Padova (PD), Italy

Institution: Department of Woman's and Child's Health, University of Padova, Padova, Italy

Institution e-mail: dipartimento.sdb@pec.unipd.it

Institution telephone number: +390498213506

Institution postal address: Via Nicolò Giustiniani 3, 35128 Padova (PD), Italy

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Abstract

Background: Food Protein–Induced Enterocolitis Syndrome (FPIES) is a non-IgE cell-mediated gastrointestinal food allergy that primarily presents in infancy, as early as the first hours of life. FPIES is often misdiagnosed as sepsis, severe gastroenteritis, abdominal surgical emergency or even metabolic, neurologic or cardiac disorders. **Methods:** We report two neonatal cases of cow’s milk protein (CMP)-induced FPIES masquerading as surgical diseases. Our purpose is to highlight the diagnostic difficulties in FPIES in this age group and to provide further evidence of the important role played by the prenatal environment in the development of allergic diseases. **Results:** Case 1 is a 2-day-old boy born at 35th+5 week of gestation admitted to our Neonatal Intensive Care Unit (NICU) for bloody diarrhea who started presenting apnea, crying, pallor, jaundice and abdominal tenderness. Case 2 is a 3-day-old boy born at 38th+5 week of gestation admitted to our NICU for repeated bilious vomiting. Both patients were administered infant formula in the first hours of life, thereafter they received only breast milk. In both cases CMP allergy was finally suspected and an extensively hydrolyzed formula was administered with resolution of symptoms. A diagnosis of CMP-induced FPIES was made. **Conclusions:** FPIES is a heterogeneous disorder. Severe forms of FPIES could be mistaken for surgical diseases, such as NEC. A trial of food elimination should be considered whenever diagnostic tests are inconclusive. FPIES must be suspected even in breastfed infants.

Keywords: FPIES; newborn; surgical disease; food allergy; cow’s milk

Word count: 2600

Introduction

Food allergy (FA) is an adverse reaction following exposure to a food due to an abnormal immunologic response to the food itself [1]. Food allergies encompass immunoglobulin E (IgE)-mediated or non-IgE-mediated mechanisms. At present, non-IgE mediated allergies are less understood than other reactions to foods [2].

Among them, Food Protein–Induced Enterocolitis Syndrome (FPIES) is a non-IgE cell-mediated gastrointestinal FA that primarily presents in infancy. It manifests as delayed onset of repetitive vomiting, often accompanied by lethargy and pallor, and/or watery or bloody diarrhea, progressing to hypotension, methemoglobinemia and acidemia in most severe cases [3,4]. Symptoms may start as early as the first days of life [5].

Once considered a rare disorder, FPIES has been increasingly diagnosed in the last decade. A large prospective birth cohort study found a cumulative incidence of confirmed cow's milk protein (CMP)-induced FPIES of 0.34% of infants born at a single hospital over 2 years [6].

Nevertheless, FPIES awareness is still low, often leading to increased morbidity from recurring episodes and extensive evaluations and hospitalizations before the diagnosis is finally considered [4].

Various presentations of FPIES occur in different populations at different ages. Therefore, FPIES is often misdiagnosed as sepsis, severe gastroenteritis, abdominal surgical emergency or even metabolic, neurologic or cardiac disorders [7].

When FPIES presents in the first weeks of life, the differential diagnosis with necrotizing enterocolitis (NEC) may be challenging, especially in the preterm population.

Hereby we report two neonatal cases of CMP-induced FPIES with onset in the first two days of life masquerading as surgical diseases. Both newborns were breastfed during the debut of symptoms. Our purpose is to highlight the diagnostic difficulties in FPIES in this age group. Moreover, we believe that our cases provide further evidence of the important role played by the prenatal environment in the development of allergic diseases.

Case 1

A 2-day-old boy born at 35th+5 week of gestation by vaginal delivery was admitted to our Neonatal Intensive Care Unit (NICU) for bloody diarrhea. Family history was negative for allergic diseases. Birth weight was 3200 g, **Apgar scores were 9 and 10 at 1 and 5 minutes, respectively**. At 1 hour of life (HOL) he was administered cow's milk (CM)–based infant formula for hypoglycemia. Thereafter he received only breast milk.

At approximately 42 HOL he passed bloody stools with mucus, hence he was transferred to NICU. Physical examination and vital signs were unremarkable. Arterial blood gas analysis revealed mixed metabolic acidosis and respiratory alkalosis with mild hyperlactatemia (lactate 2.4 mmol/L). Laboratory analysis showed only mild anemia (hemoglobin 12.7 g/dL), monocytosis (1400/mm³) and **low-normal total protein**(4.7 g/dL). Enteral feeding was suspended, and intravenous fluid therapy was started. After admission the patient kept passing bloody mucus diarrhea, alternating dark and bright red stools. Bowel movements were preceded by crying from abdominal pain. Abdominal radiograph and ultrasound were normal. Blood culture, stool culture and stool tests for rotavirus, adenovirus, *Clostridioides difficile* toxins and enterohemorrhagic *Escherichia coli* were negative.

On day of life (DOL) 3 the boy started presenting episodes of apnea, bradycardia and desaturation, most of them triggered by high-pitched crying. Cranial ultrasound showed no signs of cerebral hemorrhage. On DOL 5 physical examination revealed pallor, jaundice and abdominal tenderness. Abdominal radiograph remained negative, while repeated abdominal ultrasounds revealed mild thickening of the small bowel walls with no evidence of pneumatosis intestinalis, as well as a small amount of free intraperitoneal fluid between bowel loops. Empiric antibiotic therapy was started. As general and abdominal conditions were non-reassuring exploratory laparotomy was performed. Small and large bowel and viscera were normal. Minimal free intraperitoneal fluid with clear, light yellow appearance was aspirated and sent for culture. Mesenteric thickening with enlarged mesenteric lymph nodes was found.

Abdominal pain and tenderness receded and from DOL 7 the patient passed normal non-bloody stools. Peritoneal fluid culture and control PCR were negative, therefore antibiotic therapy was suspended. On DOL 9 enteral feeding with breast milk was gradually resumed. Despite tolerating oral intake, the baby showed poor appetite. Neonatal weight loss continued even with full parenteral nutrition.

On DOL 12, approximately 72 hours after feeding resumption the patient started passing loose bloody stools again. Crying or fussiness preceded evacuation. Physical examination revealed pallor and abdominal tenderness. Laboratory analysis showed mild anemia, monocytosis (1530/mm³) and mild eosinophilia (1390/mm³). On DOL 13 the boy developed vomit and regurgitation. Rectosigmoidoscopy up to the splenic flexure was performed, showing hyperemic, fragile, hemorrhagic rectal mucosa with superficial ulcerations. Macroscopic appearance of the sigmoid and descending colon was similar although less affected, with patchy hyperemia and small mucosal erosions. Mucosal biopsies were performed. CMP-induced colitis was suspected. The baby was started on an extensively hydrolyzed formula. Breast feeding was resumed after the mother had undergone dietary elimination of CMPs. Symptoms completely resolved within 24 hours. The patient began to thrive after a weight loss of 16% of birth weight. Rectal and colonic biopsy specimens showed mild inflammation with slight infiltrate of lymphocytes and polymorphonuclear leukocytes, including eosinophils. A diagnosis of CMP-induced FPIES was made. CM-specific serum IgE and skin prick test were negative. At 5 months of age follow-up, the boy persisted as asymptomatic, with satisfactory growth.

Case 2

A 3-day-old boy born at 38th+5 week of gestation by vaginal delivery was admitted to our NICU for repeated bilious vomiting. His mother was reportedly allergic to beta-lactam antibiotics, nickel and pork. Birth weight was 3335 g, **Apgar scores were 9 and 10 at 1 and 5 minutes, respectively**. At 3 HOL he received CM-based infant formula for hypoglycemia. Later, exclusive breastfeeding was initiated. He passed meconium within the first DOL.

At approximately 24 HOL he started presenting vomiting after each feed, alimentary at first, then bilious. Vital signs were normal. Physical examination revealed mottled

skin, jaundice and a distended abdomen, soft on palpation. Feeding was suspended and a nasogastric tube was inserted. An intravenous line was placed, and parenteral fluids were given. Blood tests showed only mild anemia (hemoglobin 12.6 g/dL), eosinophilia (910/mm³) and monocytosis (1470/mm³). Intestinal obstruction was suspected, but abdominal radiograph was normal, with the exception of a small air-fluid level within the stomach. Broad-spectrum empiric antibiotic therapy was started. Blood culture, stool culture and stool tests for rotavirus and adenovirus were found negative.

On DOL 3 vomiting had ceased and patient was well-appearing, therefore feeding with breast milk was gradually resumed. Vomiting recurred, nonprojectile, non-bilious, occurring 2-3 hours after each feed. Stool output maintained normal. The baby appeared pale, fussier, with decreased activity. Abdominal ultrasound and upper and lower gastrointestinal series revealed no evidence of intestinal malrotation or other anatomical abnormalities. Cranial ultrasound showed mild periventricular white matter hyperintensities but otherwise normal brain structures. Urinalysis was normal. Vomiting and accompanying signs and symptoms once again ceased with feeding interruption and recurred with feeding resumption on DOL 6.

CMP allergy was suspected, and an extensively hydrolyzed formula was administered with prompt resolution of vomiting and other clinical symptoms.

The mother underwent dietary elimination of CMPs, then breastfeeding was resumed without further problems.

A diagnosis of CMP-induced FPIES was made. CM-specific serum IgE were negative.

At 4 months of age follow-up vomiting had not recurred. The boy was still breastfed, the mother being on a strict CMP-free diet. Weight gain and linear growth were found adequate for his age.

Discussion

Over the last three decades there has been a dramatic increase in the prevalence of FA, which has now reached epidemic numbers. Changes that have occurred in both lifestyle and environment have contributed to this phenomenon [8]. Neonates, both premature and full-term have been likewise affected by this trend [9].

Immune system reprogramming occurring during in utero development and prenatal sensitization could be held responsible for FA occurring in the newborn, in the first days or even hours of life, even before any oral intake of the allergen itself [9-18]. Evidence suggests that during prenatal life the individual is sensitive to environmental exposures [19]. Furthermore, detection of allergens in the amniotic fluid and fetal blood has provided evidence of intrauterine allergen exposure through transamniotic and transplacental transfer [20]. If the inductive phase of allergic reaction takes place during intrauterine life, the effector phase occurs after postnatal re-encounter with the allergen. Early exposure to CMPs acts as a challenge to already-sensitized newborns. In addition, the immaturity of the gastrointestinal tract, especially in preterm babies, may result in increased uptake

of food allergens. This is further heightened when the intestinal epithelium is disrupted by multiple insults, such as hypoperfusion or fasting [9]. On the other hand, extremely and very preterm newborns hardly develop FA, being immune-immature. FA requires maturation of the immune system, particularly of Th2-type adaptive immune response occurring at around 30-32 weeks of corrected gestational age [21].

Our cases constitute different examples of very early onset CMP allergy. CMP allergy is the most common FA in infants and newborns [22-24]. Most neonatal CM allergies are non-IgE-mediated and encompass different disorders affecting the gastrointestinal tract, including FPIES, food protein-induced allergic proctocolitis (FPIAP), food protein-induced enteropathy (FPE) [2].

Both our patients were diagnosed with CMP-induced FPIES. Distinguishing feature of FPIES are a lack of evidence of IgE sensitization and relapse of symptoms on reintroduction of the offending food, as demonstrated in our patients. FPIES diagnostic criteria focus on systemic impairment and severe presentation [3,25]. These are not a feature of FPIAP and FPE. FPIAP manifests with bloody stools in otherwise well-appearing young infants. Features of FPE are nonbloody diarrhea and malabsorption; symptoms resolve usually slowly, within 1 to 4 weeks after elimination of the trigger food [2].

Clinical phenotype of Case 1 can be traceable to chronic FPIES, despite its short course. Bloody diarrhea, intermittent emesis and failure to thrive are characteristic signs of so-called chronic FPIES. Resolution of symptoms within days after elimination of the culprit food and recurrence when the food is reintroduced, as happened in this case, is the most important criterion for diagnosis of chronic FPIES [3].

The patient described in Case 2 was diagnosed with acute FPIES, whose major diagnostic criteria is the appearance of repetitive vomiting approximately 1-4 hours after ingestion of the offending food, together with lethargy, pallor and sometimes hypotension. Signs of IgE-mediated allergy, such as hives or wheezing are absent. Symptoms completely resolve over a matter of hours and the patient is asymptomatic when the trigger food is withdrawn, as was the case with the patient. The boy had a family history of allergic disease, which is common among FPIES subjects [5].

Both neonates were breastfed after receiving a small amount of CM-based infant formula within the first hours of life. FPIES in exclusively breastfed infants is rare [5]. Nevertheless, the presence of antigenically intact CMPs in breast milk of mothers who consume CM has already been proven [26]. The mothers of the two patients consumed CMPs daily. The same cannot be said for certain of breast milk bank donors. The threshold dose of a given trigger food is variable, possibly very low and may sometimes be lacking altogether in breast milk, depending on the maternal diet. This might explain the slow recurrence of symptoms after resumption of enteral feeding in the first patient.

In both clinical cases, diagnosis of FPIES posed a significant challenge to the neonatologists and surgical diseases were suspected in the first place. Symptoms of FPIES are often nonspecific, especially in preterm infants. Lethargy, paleness, feeding intolerance, abdominal distension, and bloody stools are common to potentially life-

threatening conditions such as sepsis and surgical diseases. Workup often leads to invasive evaluations, such as endoscopy and laparotomy, as was the case with the first patient [5].

FPIES could masquerade as NEC, as happened in Case 1. A recent paper [27] retrospectively reviewing all cases of NEC in a neonatal intensive care unit found that 5 out of 56 preterm infants diagnosed with NEC had an atypical course, with clinical findings more consistent with FPIES. The authors proposed that FPIES can sometimes mimic NEC, given the overlap in clinical presentation and the lack of pathognomonic diagnostic tests for both disorders. Not even the radiological finding of pneumatosis intestinalis is specific of NEC, occasionally being present in FPIES [14].

Regarding the second patient, intestinal atresia and malrotation were prime suspects. Bilious vomiting is attributed to intestinal obstruction until proved otherwise [28]. We hypothesized that bile vomit resulted from duodeno-gastric reflux due to retroperistalsis induced by vomiting.

In both cases diagnosis of FPIES was primarily based on the rapid improvement of signs and symptoms after withdrawal of CMP exposure and on reproducibility of reactions with reintroduction. We did not perform oral food challenge (OFC), which is regarded as the gold standard diagnostic test. According to international consensus guidelines, however, OFC is not required in presence of a convincing history of FPIES, especially when its risk might outweigh its benefit [3]. There is no laboratory test specific for FPIES. Some patients demonstrate eosinophilia, as in our cases. However, an increase in eosinophil count is non-specific, being frequently found in sick neonates [16]. **Stool examination can reveal eosinophils, eosinophilic debris and/or neutrophils; however, results are nonspecific and should not be used to diagnose FPIES [3].** Endoscopy evaluation is not required in patients with suspected FPIES, but might be revealing, as in Case 1.

Both patients were managed with dietary elimination, which is the mainstay of treatment [3]. This involves a hypoallergenic formula or alternatively, a CM-free diet for the breastfeeding mother.

The prognosis is generally good. The average age of tolerance to CM is approximately 3 years [3].

Conclusions

FPIES is a heterogeneous disorder possibly combining a spectrum of different phenotypes [3]. Our cases show different clinical presentations of the same disease in two newborns. CMP-induced FPIES can present in term and preterm neonates as early as the first days of life. This age of onset suggests the presence of intrauterine sensitization.

Severe forms of FPIES could be mistaken for surgical diseases, such as NEC. Routine evaluation must be undertaken anyway, given the significant morbidity and mortality associated with surgical disorders. However, a trial of food elimination should be considered whenever gastrointestinal and systemic signs and symptoms persist despite medical therapy or when diagnostic tests are inconclusive. FPIES must be suspected even in breastfed infants. Additional studies are needed to refine diagnostic methods and to improve disease treatment and prevention.

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