Food Protein-induced Enterocolitis Mimicking Necrotizing Enterocolitis in a Premature Infant: Case Report

Food protein-induced enterocolitis (FPIES) is not well documented in newborns. Although FPIES is rare in premature infants, it may occasionally be confused with necrotizing enterocolitis (NEC). This is particularly true for low birth weight infants admitted to the neonatal intensive care unit. We report a case of cow’s milk protein-induced enterocolitis mimicking recurrent NEC in a premature infant. The patient presented bloody stools, abdominal distension, pneumatosis intestinalis, peripheral eosinophilia, and successful resolution of the symptoms upon modification of the diet to an amino acid-based formula. We aim to highlight that although the prevalence of FPIES is relatively rare in premature infants, clinicians should lead to consideration of FPIES in NEC-like illness.

Key Words: Food allergy, Milk proteins, Necrotizing enterocolitis, Premature infant

Introduction

Food protein-induced enterocolitis (FPIES), a non–immunoglobulin E (IgE)–mediated syndrome resulting in hypersensitivity to food antigens, is an inflammatory gastrointestinal process that affect 3% to 7% of healthy infants during the first year of life. The most common food triggers are cow’s milk and soy proteins. Although FPIES is rare in newborns, more than 20 cases who were diagnosed to FPIES during neonatal period have been reported. The incidence and clinical manifestations of FPIES in premature infants with comorbidities remains poorly identified. Reports in premature infants described cases of hematochezia and enterocolitis while receiving intact milk protein that resolved with its elimination and recurred with its reintroduction. Necrotizing enterocolitis (NEC) is the most common life-threatening medical and surgical emergency in premature infants. Therefore, NEC is the first concern when premature infants present with hematochezia or feeding intolerance. In this article we report a case of FPIES mimicking NEC in a 27-week-old premature infant whose symptoms resolved by the elimination of milk protein in the diet.

Case

A male preterm infant was born at 27 weeks and one day of gestation with a birth weight of 1,100 g. The medical issues during hospitalization included a respiratory distress syndrome, apnea of prematurity, hyperbilirubinemia, bronchopulmonary dysplasia, feeding intolerance, and total parenteral nutrition associated cholestasis. There was no intraventricular hemorrhage, and patent ductus arteriosus was closed after medical treatment at 15 days of birth. Meconium passage occurred within 24 hours of birth. Trophic feeding was started on the 1st day of life (DOL) with a preterm formula. Enteral feeding was gradually increased to 30 mL/kg/day...
on DOL 10. On DOL 11 (28 weeks and 5 days of postmenstrual age, PMA), DOL 24 (30 weeks and 4 days PMA), and DOL 31 (31 weeks and 4 days PMA), the patient developed large gastric residuals and had episodes of abdominal distension after feeding with the preterm formula and expressed breast milk (EBM). At each episode, the first clinical impression was NEC, therefore enteral feeding was stopped and broad spectrum antibiotics were treated repeatedly after multiple sepsis workups were conducted.

On DOL 45 (33 weeks and 4 days PMA), the patient was referred to the neonatal intensive care unit (NICU) of our institution for an emergent surgical operation on the marked abdominal distension (Fig. 1A). Intraoperatively, a 10 cm ileo-ileo intussusception was discovered. It required a small bowel resection and anastomosis, approximately 30 cm proximal to the ileocecal valve. Other parts of the intestine were grossly non-necrotic and viable. The biopsy report showed a transmural hemorrhagic infarction and increased eosinophilic infiltration at the mucosa (Fig. 1B).

On DOL 52 (34 weeks and 4 days PMA), enteral feeding was restarted with either a preterm formula or EBM at 30 mL/kg/day. Unfortunately, abdominal distension and emesis developed. After two days of bowel rest, continuous infusion of a preterm formula was restarted. However, the patient, once again, developed emesis.

Transpyloric tube was inserted in NICU by neonatologist and the position of transpyloric tube was confirmed by abdominal X-ray. Transpyloric feeding was initiated on DOL 60 (35 weeks and 5 days PMA) with an extensively hydrolyzed milk formula (HA®; Maeil Dairies Co. Ltd., Seoul, Korea) for feeding intolerance. Full enteral feeding was performed on DOL 70.

On DOL 75 (37 weeks and 6 days PMA), the patient developed abdominal distension again. This was now associated with large, grossly bloody stools. An abdominal X-ray and an abdominal ultrasonography were performed. These revealed pneumatosis intestinalis, distended bowel loops, wall thickening, and portal venous gas formation (Fig. 2). The laboratory findings included a white blood cell count of 4,520/mm³, hemoglobin of 8.5 g/dL, a platelet count of 298,000/mm³, albumin of 2.4 g/dL, C-reactive protein of 0.78 mg/dL (0.5 mg/dL, cut-off value), and a fecal calprotectin of 846.7 mg/kg (50 mg/kg, cut-off value). The initial clinical impression was NEC. However, the C-reactive protein was consistently negative at all short-term evaluations. No leukopenia, thrombocytopenia, and metabolic acidosis developed during the follow-up evaluations. The baseline peripheral eosinophil count was 4%, and then showed a gradual increase with time to 11.3% at 3 days of illness. Clinically, the patient appeared well and had stable vital signs. Evaluations for bacterial and viral sepsis were performed repeatedly. These all came out as negative. We noted that the patient’s clinical condition was not compatible with NEC. The case described had clinical findings which were more consistent with the diagnosis of FPIES. The serum

![Fig. 1. Abdominal radiography showing marked bowel dilatation on the 45th day of life (33 weeks and 4 days of postmenstrual age) (A). High power view of the small intestine shows increased eosinophilic infiltration (12 eosinophils/HPF, arrows) at the mucosa. Hematoxylin and eosin stain [H&E, x400] (B).](image-url)
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Fig. 2. Diffuse bowel dilatation with pneumatosis (black arrows) on the 75th day of life (37 weeks and 6 days of postmenstrual age) at abdominal radiography (A) and abdominal ultrasonography (B). The portal vein gas (white arrows) is seen through the abdominal ultrasound (C).

Discussion

This report presents a case of cow’s milk protein–induced enterocolitis in a preterm infant with laboratory and radiologic findings mimicking recurrent NEC–like illness. Clinical diagnosis of FPIES was made with a successful resolution of symptoms after the modification of the diet with an amino acid–based formula. This case was a severe form of FPIES because the disease progressed despite feeding with an extensively hydrolyzed formula.

FPIES is triggered by a non–IgE–mediated food hypersensitivity. The exact underlying mechanisms of FPIES, however,
are not clearly understood.\textsuperscript{1-3} Data suggest that the innate immune system and T cells become activated once exposed to food antigens.\textsuperscript{4} Increased levels of tumor necrosis factor–α and decreased expression of transforming growth factor–β receptors have also been noted in the intestinal mucosa of patients with FPIES.\textsuperscript{13-15} The most common food triggers in FPIES are cow’s milk and soy proteins.\textsuperscript{9} Thus, reactions may occur with infant formulas. FPIES typically presents in first months of life. A patient may have vomiting, diarrhea, abdominal distension, bloody stools, or lethargy within 1–4 weeks after initial exposure to a triggering antigen.\textsuperscript{1,16} The incidence of FPIES in neonates especially in preterm infants is not well documented.\textsuperscript{5-9} Similar symptoms are sometimes associated with the initial presentations of NEC in preterm infants. NEC may occur at any time; however, it is mostly commonly observed near 32 weeks of gestation. On the other hand, symptoms associated with FPIES rarely develop before 6 weeks of life.\textsuperscript{10,11} Although an oral food challenge is the most conclusive diagnostic method, it has been associated with risk of systemic reactions.\textsuperscript{1,2,16} Thus, the diagnosis is suspected based on the clinical presentations as vomiting, diarrhea, bloody stool, abdominal distension, pneumatosis intestinals, and clinical resolution of symptoms to elimination of dietary protein.\textsuperscript{3-5} These clinical suspicions match the findings of this case. Although laboratory findings alone cannot confirm the diagnosis of FPIES, peripheral eosinophilia is a common hematologic abnormality observed.\textsuperscript{1} A recent study reported that cases initially diagnosed as NEC may be more consistent with FPIES if these cases have less leukopenia, more eosinophilia, less thrombocytopenia, and less CRP elevation.\textsuperscript{1,4,7} Gradual increase of peripheral eosinophilia (11.3%) was the only abnormal laboratory finding in this case. It developed together with the clinical symptoms and correspondingly decreased (2%) after modification of the diet to an amino acid–based formula.

The clinical course of FPIES is relatively benign. On the other hand, NEC has a poor prognosis. It is therefore important to discern FPIES from NEC because the treatment strategies of these two diseases are very different. With NEC, treatment modalities have focused mostly on stopping enteral feeding, broad spectrum antibiotics.\textsuperscript{10,11} In contrast, the management of FPIES is dietary modification.\textsuperscript{16}

With regards to the occurrence of intussusception before the patient was diagnosed with FPIES, there have been a few documented cases of non–IgE–mediated food allergy accompanied by intussusception in the literature.\textsuperscript{17,18} However, FPIES presenting as intussusception has not been reported in neonates so far. Intussusception in premature infants has been reported primarily in relation to NEC.\textsuperscript{19} In this case, the recurrent clinical symptoms, acute onset of intussusception, and increased eosinophilic infiltration at the mucosa initially caused the misdiagnosis of NEC. However, the diagnosis of FPIES was eventually reached after further evaluation. These findings led us to hypothesize that the mucosal edema caused by the allergic inflammatory reaction could have resulted to the formation of an intussusception. Based on this premise, further researches about atypical cases of intussusception in preterm infants need to be conducted.

In conclusion, although the prevalence of FPIES is relatively rare in premature infants, clinicians should lead to consideration of FPIES in NEC–like illness with atypical clinical course, a late–onset, episodic recurrences, the presence of peripheral eosinophilia, and resolution with dietary modifications.

Conflict of Interests

No potential conflict of interest relevant to this article was reported.

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