Food Protein-Induced Enterocolitis Syndrome Masquerading as Sepsis in Early Infancy

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ABSTRACT

Food protein-induced enterocolitis syndrome (FPIES) is a less common etiology of vomiting in an infant and can be challenging to diagnose. The absence of confirmatory laboratory testing or clear clinical criteria and signs/symptoms that overlap with other entities can lead to instances of misdiagnosis. We present a case of an exclusively breastfed infant who presented with emesis and dehydration. The infant was initially diagnosed with and treated for sepsis but was eventually diagnosed with FPIES. We discuss challenges in making a diagnosis of FPIES and potential factors that can distinguish it from sepsis.

KEYWORDS: food protein-induced enterocolitis syndrome (FPIES); neonatal sepsis; dehydration; vomiting; immunoglobulin E (IgE)

INTRODUCTION

The differential diagnosis for a vomiting, ill-appearing infant is broad and can prompt extensive work-up. More common infectious diagnoses are infectious gastroenteritis and bacterial sepsis. Anatomical causes can include pyloric stenosis, volvulus, and intussusception, among others. More rare presentations include Hirschsprung disease, necrotizing enterocolitis, metabolic disorders, and allergic disorders such as anaphylaxis, eosinophilic esophagitis, and food protein-induced enterocolitis syndrome (FPIES).[1,2] FPIES is a non-IgE-mediated food hypersensitivity reaction that ranges in severity of presentation, with 15–20% of cases leading to hypovolemic or distributive shock.[3,4] The pathophysiology is poorly understood. In 2017, diagnostic criteria for acute FPIES were published, but those for chronic FPIES remained quite broad—vomiting and/or diarrhea to varying clinical degrees after ingestion of an offending food.[3] Regardless of degree of presentation, symptoms should resolve after removing the offending food.[3] Given this fairly non-specific criteria, diagnosis is often delayed, and patients are often initially misdiagnosed with other conditions. We report a case of an exclusively breastfed infant who presented with dehydration and emesis. Based on initial laboratory studies and exam, she was initially thought to have, and was treated for, sepsis, but was ultimately diagnosed with FPIES.

CASE PRESENTATION

The patient is a 44-day-old female with sickle cell trait who presented to the emergency department with approximately one week of vomiting, dehydration, and weight loss.

Six days prior to presentation, the patient began spitting up with feeds, which was unusual for her. This gradually progressed to larger, more frequent non-bloody non-bilious emesis, vomiting two to three ounces of breastmilk after each feed. Parents also noted mild non-bloody diarrhea over the prior several days. Parents denied recent sick contacts, rhinorrhea, cough, or congestion.

The patient was born at 40 weeks gestation via cesarean section for fetal distress. Delivery was complicated by meconium-stained amniotic fluid and maternal fever during birth. The patient had no respiratory distress at birth, did not require sepsis rule-out, and did not require NICU admission. The patient's mother was diagnosed with postpartum endometritis requiring hospital stay and intravenous antibiotics. Sickle cell trait was identified on newborn screen, but the patient had otherwise been healthy.

She was exclusively breastfed and gained weight well in the first weeks of life. Her mother reportedly had a good breast milk supply. However, weight gain gradually slowed over the two weeks prior to presentation and weight eventually declined, with a notable weight loss of two ounces over the three days prior to presentation. She initially presented to her pediatrician, who ordered an abdominal ultrasound to rule out pyloric stenosis, which was normal. Continued weight loss, more frequent non-bloody non-bilious emesis, and the start of slightly watery stools prompted presentation to the emergency department.

In the emergency department, the patient was fussy but consolable with evidence of dehydration and delayed capillary refill on exam. Lungs were clear to auscultation, no rashes or vesicles noted, and abdomen was soft, non-tender, and nondistended without palpable masses. Given vomiting and poor growth, the pediatric gastroenterology team was consulted and recommended laboratory work-up. Initial labs were significant for leukocytosis with bandemia and elevated C-reactive protein of 46.67 mg/L. While in the emergency department, she gradually became more ill-appearing, with evidence of hypothermia and poor perfusion. Initial labs and worsening clinical status prompted a full septic work-up including blood, urine, and cerebrospinal fluid (CSF) studies.

Urinalysis was without pyuria but with evidence of dehydration. CSF studies were unremarkable. Respiratory and stool infectious panels were negative. Given concern for sepsis with hypothermia, tachycardia, and hypotension, leukocytosis with bandemia, and elevated inflammatory markers, the patient was started on ceftriaxone monotherapy at meningitic dosing and admitted for 48-hour sepsis rule out. Intravenous fluids were initiated for hydration in the setting of continued large-volume emesis after breastmilk feeds and worsening diarrhea.

Blood, urine, and CSF cultures remained negative at 48 hours, so antibiotics were discontinued. Speech Language Pathology was consulted given feeding concerns. Intake improved slightly with transition to different nipple and oral electrolyte solution. Given her negative infectious work-up and lack of improvement on antibiotics, suspicion increased for gastrointestinal concerns including milk protein allergy. An amino acid-based formula was started on hospital day four. On hospital day five, the patient continued to have feeding intolerance with worsening non-bloody diarrhea, and she became more ill-appearing and lethargic. She also became febrile, prompting repeat labs revealing significant electrolyte derangements (hypernatremia, hypokalemia, hyperchloremia), leading to transfer to the intensive care unit (ICU).

Given persistent vomiting and diarrhea, FPIES with possible bacterial translocation was high on the differential. The pediatric infectious disease team was consulted and recommended initiation of ceftriaxone and metronidazole. The pediatric gastroenterology team was consulted and recommended bowel rest and initiating parenteral nutrition.

In the ICU, she required continued electrolyte replacement. Stool output gradually slowed with bowel rest and parenteral nutrition. Repeat infectious studies were negative at 48 hours, so antibiotics were discontinued. Additional work-up revealed fecal calprotectin >3000 mg/kg, fecal elastase 68 ug/g. Clinical improvement with removal of trigger food (breastmilk, milk protein) suggested a diagnosis of FPIES.

After a period of bowel rest, the patient gradually tolerated Pedialyte and subsequently full enteral nutrition with an amino acid-based formula. She was ultimately discharged home with pediatric gastroenterology follow-up.

DISCUSSION

This case is an example of a particularly challenging diagnosis of FPIES in an exclusively breastfed infant who presented with clinical symptoms of sepsis.

FPIES typically presents within the first year of life when a new formula or food is introduced that triggers a reaction. The severity depends upon the amount and frequency of intake of the trigger food.[3] FPIES in children can be acute or chronic. In 2017, the "International consensus guidelines for the diagnosis and management of [FPIES]" were published, detailing major and minor criteria for acute FPIES but only a categorical description of chronic FPIES.[3] Acute FPIES is more common, presenting with acute onset emesis within several hours of ingesting the trigger food with or without associated lethargy, pallor, and diarrhea. Chronic FPIES is characterized by gradually worsening emesis or diarrhea over days to weeks and typically occurs when the trigger food is ingested regularly. It can be associated with poor weight gain or growth faltering. The diagnosis of chronic FPIES is typically confirmed by a trial of reintroduction of the trigger food thought to be leading to acute onset vomiting and diarrhea. Without this trial, the diagnosis remains presumptive.[3,4]

Because FPIES is a clinical diagnosis with poorly understood pathophysiology and no known biomarker for confirmatory testing, the diagnosis is often delayed and patients are often misdiagnosed with other conditions.[2,3,5] The case presented is an example of a delayed diagnosis of FPIES in which the patient was initially diagnosed with sepsis, no bacterial source was confirmed, and she did not recover until replacement of breast milk with amino acid-based formula. FPIES and sepsis share many clinical and laboratory features. Both can present with weakness, lethargy, vomiting, tachycardia, and hypotension, and both can be associated with leukocytosis with neutrophilia, thrombocytosis and metabolic acidosis.[2,5]

Lee et al conducted a retrospective case study attempting to identify distinguishing factors between acute FPIES and common mimickers including bacterial sepsis and gastroenteritis.[5] They found clinical features to be most helpful in identifying the diagnosis. While vomiting is common in all three, they found lethargy and pallor to be more commonly associated with FPIES, whereas diarrhea is more common in bacterial sepsis and gastroenteritis. Fever and elevated CRP were more predictive of sepsis and gastroenteritis.[5] However, another study found fever and elevated CRP to be present in at least one third of patients with FPIES.[6] In any case where fever or hypothermia is present, it is important that sepsis is first ruled out before consideration of alternative diagnoses. In the absence of a confirmatory biomarker or laboratory test, FPIES will likely remain a challenging diagnosis to make. Of note, in the present case, stool calprotectin was notably high and fecal elastase was low. While these studies are not always obtained when suspecting FPIES, the values noted in this case are not unusual in a patient with profuse diarrhea, which can lead to intestinal inflammation (and thus elevated stool calprotectin) and low fecal elastase (due to dilutional effect).

Another unique element of this case that made diagnosis challenging is that the infant was exclusively breastfed at the time of presentation. Several studies have shown that only about 5% of infants diagnosed with FPIES were exclusively breastfed at the time of presentation.[7,8] Mild FPIES in

an exclusively breastfed infant can be managed with transition to an extensively hydrolyzed formula (and sometimes, mothers can implement an exclusion diet). However, in severe cases like the one presented here, an amino acid-based formula is generally the preferred management.[9]

CONCLUSION

When evaluating an ill-appearing infant presenting with emesis, the initial differential diagnosis is broad and includes several potentially serious conditions that require rapid diagnosis. It is important to consider FPIES as a potential cause of this presentation, especially in cases where a child has unexplained refractory hypovolemic shock despite appropriate empiric therapy. FPIES will likely remain a challenging diagnosis to make given the clinical nature of the diagnosis and the absence of confirmatory testing.

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Disclosures

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