Kobe J. Med. Sci., Vol. 67, No. 1, pp. E7-E9, 2021

Markedly Elevated Procalcitonin in Food Protein Induced Enterocolitis Syndrome

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Received 17 November 2020/ Accepted 6 January 2021

Keywords: milk, oral food challenge test, bacterial sepsis, C-reactive protein

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal food allergy. Some studies have reported that FPIES was associated with elevated C-reactive protein (CRP). However, the number of reports on the relationship between FPIES and procalcitonin (PCT) is limited. This case report highlights the fact that PCT levels can be markedly elevated in patients with acute FPIES. An 11-month-old girl previously diagnosed with FPIES underwent an oral food challenge test (OFC). Her serum PCT levels were measured after she developed severe symptoms including fever and shock following administration of 100mL of formula milk. The PCT levels were extremely elevated but improved without antibiotics the next day. The fact that serum PCT levels may be significantly elevated in FPIES means that differentiating severe FPIES from sepsis could be more challenging than was previously thought.

INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal (GI) food allergy that typically presents during infancy(7). Acute FPIES causes vomiting, diarrhea, and/or bloody stools. Furthermore, approximately 15% of patients with acute FPIES present with shock and require aggressive fluid resuscitation(7). Such patients are often transported to emergency departments and misdiagnosed with sepsis. The laboratory data findings in acute FPIES are nonspecific. Some studies have reported that FPIES was associated with neutrophilia, thrombocytosis, methemoglobinemia, metabolic acidosis, and elevated C-reactive protein (CRP). However, the number of reports on the relationship between FPIES and procalcitonin (PCT) is limited. Here, we report a case of FPIES in which the patient presented with fever, shock, and highly elevated PCT levels that were caused by the administration of infant formula milk.

CASE REPORT

A female neonate, who was born at 37 weeks and 5 days of gestation and weighed 3318 g, was administered formula milk 6 hours after birth. Mildly bloody stools were observed 13 hours after birth. The same formula milk was continued under close monitoring. The bloody stools subsided temporarily on day 3. On day 9, however, she again developed bloody stools accompanied by vomiting, weight loss (2976 g on day 9), metabolic acidosis (venous blood gas: pH 7.264, pCO2 40.7 mmHg, HCO3 18.0 mEq/l), and an elevated CRP (10.2 mg/L). After the formula milk was changed to an amino-acid-rich elemental diet, Elental® P (EA Pharma, Tokyo, Japan), her symptoms improved. At 2 months of age, she underwent an oral food challenge test (OFC) with 100 mL of the same formula milk that had caused the original GI symptoms. The result of the OFC was positive, and vomiting was observed 4 hours after ingestion of the formula milk. Since she was in a stable condition after vomiting, sepsis was not suspected and blood tests were not done. The allergen-specific lymphocyte stimulation test was positive, and the maximum reaction (count per minute/stimulation index) for lactoferrin and β casein was 3395/7.45 and 3382/7.42, respectively (control reaction 456). A skin prick test for milk allergens was negative. Therefore, she was diagnosed with FPIES due to formula milk. At 11 months of age, she underwent a second OFC using the same amount of formula milk. After the test, she developed fever, tachycardia, vomiting, diarrhea, pallor, and a mildly reduced level of consciousness. The clinical and laboratory data on the day after the second OFC test are shown (Table I). Of particular note are the markedly elevated serum PCT levels. Antibiotics were not prescribed at this point, and after adequate administration of intravenous fluid, her condition improved the following day.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Table **I** Clinical and laboratory data

	23 hours after OFC	38 hours after OFC
Vital signs		
Axillary temperature (°C)	38.1	36.8
Heart rate (bpm)	187	118
Complete blood count		
White blood cells (/μL)	14,960	14,020
Segmented (%Leukocytes)	64.5	36.5
Stab (%Leukocytes)	2.0	1.5
Eosinophils (%Leukocytes)	2.0	0.0
Hemoglobin (g/dL)	13.5	10.2
Blood biochemistry		
CRP (mg/L)	106.3	35.3
PCT (ng/mL)	91.99	39.86
BUN (mg/dL)	56.1	22.4
Creatinine (mg/dL)	0.54	0.35
Venous blood gas		
pH	7.325	7.425
pCO2 (mmHg)	30.3	30.5
HCO3 (mmol/L)	15.3	19.7
Methemoglobin (%)	2.4	0.7
Stool test		
Fecal occult blood	Positive	
Stool antigen test		
Rotavirus	Negative	
Adenovirus	Negative	
Norovirus	Negative	
Bacteriological examination		
Blood culture	Negative	

DISCUSSION

This case suggests that serum PCT may be markedly elevated in FPIES. Unlike IgE-related food allergies, FPIES can be accompanied by fever and elevated CRP. Fever is observed in 13% of FPIES patients at initial presentation(7). Moreover, 61.1% and 33.3% of FPIES cases show increased CRP and CRP levels >20 mg/L, respectively(4). Additionally, elevated CRP levels were observed in FPIES patients who presented with fever(4). Fever and elevated CRP levels often indicate infection and sepsis, which is one of the main differential diagnoses of FPIES. PCT, on the other hand, has been proposed as a more characteristic marker of systemic inflammation than CRP(8). However, there have been only two international reports on FPIES with elevated PCT till date(2,9). In this clinical case, the PCT levels observed were much higher than those reported in those studies (3.84 ng/mL and 15.58 ng/mL)(2,9). Differentiating severe FPIES from sepsis could be more challenging than was previously thought, in other words, patients with FPIES who present with fever and a high PCT are more likely to be misdiagnosed with sepsis.

It is unclear how FPIES leads to elevated PCT levels. A recent paper reported that interleukin-6 (IL-6) was elevated 6 hours after ingesting allergenic food in patients with FPIES(1). PCT levels increase in the presence of pro-inflammatory cytokines, such as IL-1, IL-6, or tumor necrosis factor α. This is most likely due to inhibition of PCT proteolysis(5). These cytokines are also involved with raised CRP levels and CRP levels are known to be elevated in FPIES. A similar mechanism is presumably responsible for the increase in PCT levels. On the other

hand, PCT is reported to be more accurate for the diagnosis of sepsis than CRP(10). However, it should be noted that no matter how high the PCT is, there are cases of non-sepsis, as in this case.

In this case, serum PCT levels were not taken prior to the OFC due to the infant being in good general condition at the time. The PCT levels were confirmed as decreased on the second day after the OFC without antibiotics. From this clinical course, it is almost certain that the increase in PCT value was due to the formula milk.

A variety of protocols for FPIES-related OFCs have been published(7). The current consensus is to administer the challenge food at a dose of 0.06 to 0.6 g (usually 0.3 g) of the food protein per kilogram of body weight. Although low dose OFCs are safer, patients have to undergo repeated OFCs, which increases hospital visits. In this case, due to family circumstances, the patient's parents opted for a single high dose OFC. Through a process of fully informed consent and shared decision-making, a dose of 0.6 g of milk protein per kilogram of body weight (100mL of formula milk) was chosen for the first OFC. There is data that suggests that in patients with milk-induced FPIES, 60% develop tolerance by 1 year of age(3). For this reason, the same amount of formula milk (100mL) was prepared for the second OFC. As a result, both doses were near the upper limit of the recommended dosage range. According to Japanese FPIES consensus recommendations, performing serial OFCs daily over the course of two weeks with a starting milk load of 0.5 mL/kg and increasing gradually to 20 mL/kg is thought to be safer than a single high dose OFC(6). It is possible that this patient’s severe reaction may have been prevented using this low dose OFC strategy.

In conclusion, PCT may be highly elevated in patients with FPIES. It is difficult to distinguish FPIES from sepsis by examining laboratory data alone, and FPIES should be considered as a differential diagnosis in patients with markedly elevated PCT levels.

ACKNOWLEDGMENTS

None of the authors has any conflicts of interest or any financial ties to disclose.

The authors would like to thank Noel Hauser, Hyogo Prefectural Tamba Medical Center, for providing constructive advice and Editage (www.editage.com) for English language editing.

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