



Clinical Notes

Atypical food protein-induced enterocolitis syndrome after vaccinations

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Food protein-induced enterocolitis syndrome (FPIES) is a non-immunoglobulin (Ig) E-mediated gastrointestinal food allergy that typically shows acute and chronic phenotypes.¹ The acute form, which is characterized by repeated vomiting, lethargy with pallor, and diarrhea within 2–6 hours from food intake, is the most common type. Patients with chronic FPIES present intermittent emesis, watery diarrhea, dehydration, acidemia, failure to thrive, hypoalbuminemia and weight loss. An acute-on-chronic phenotype also exists in which neonates initially present with chronic FPIES but present with acute FPIES on accidental “on-off” exposure.^{1,2} Nonspecific symptoms and lack of definitive diagnostic tests sometimes delay the diagnosis. Here we describe the case of an infant who presented with atypical FPIES with severe hypoalbuminemia 2 days after multiple booster immunization.

The patient was a Japanese boy who was born with an Apgar score of 9/10 by cesarean section at 40 weeks and 0 days of gestation due to abruptio placentae. His birthweight was 3,480 g, and his birth height was 45.7 cm. Dextrocardia was unexpectedly detected at 1 month of age by a routine checkup by a pediatrician. Further evaluation revealed no other major anomalies. He was appropriately breast-fed with normal growth and development. His mother had no food habits. A regular checkup by a pediatrician revealed no problems, and the boy had a bodyweight of 4,356 g at 30 days of age, and 4,730 g at 50 days of age. He transiently showed growth failure, with a bodyweight of 4,670 g at 72 days, probably due to a shortage of breast-feeding. Breastfeeding was continued with the addition of baby formula, and his weight increased to 5,295 g at 79 days of age. In this time, he received routine immunization with *Haemophilus influenzae* type b (Hib) vaccine (primary and first booster injections), pneumococcal conjugate vaccine (PCV) (primary and first booster), diphtheria-tetanus-pertussis and inactivated poliovirus vaccine (DTP-IPV) (primary), hepatitis B vaccine (HBV) (primary) and rotavirus

vaccine (primary, Rotarix® – RV1) by 100 days of age without any problems. At around 120 days of age, he sometimes refused formula feeding. At 133 days of age he received the second boosters of DTP-IPV, HBV, and rotavirus vaccine. Two days later, he started frequent vomiting and diarrhea. A clinic was consulted; however, the vomiting and diarrhea persisted for several days with conventional treatment. Eight days later, poor activity with severe hypoalbuminemia (serum albumin level of 1.6 g/dL) with weight loss (5.9 kg) were detected by the primary pediatrician and the boy was admitted to our hospital. Under treatment with intravenous fluid administration with nothing by mouth, the vomiting and diarrhea disappeared after a few days. A rotavirus antigen test was negative. On day 19 of the illness, oral nutrition with medium chain triglycerides (MCT) formula was started because it was recommended as dietary therapy for protein-losing enteropathy (PLE), and frequent vomiting appeared just 2.5 hours after the trial. From day 26 of illness, the oral intake of amino acid formula (Elen-tal P®) was started without gastrointestinal symptoms. ^{99m}Tc-diethylene triamine pentaacetic acid human serum albumin (^{99m}Tc-HAS-D) scintigraphy did not show positive findings, suggesting PLE. Alpha-1 antitrypsin clearance was within normal range. Esophagogastroduodenoscopy revealed a normal appearance, whereas colonoscopy revealed multiple small nodular lesions with vascular dilations in the sigmoid colon. A histopathological examination detected eosinophils in the duodenum and sigmoid colon. The duodenum was shortened with widened villi. The sigmoid colon was demonstrated the presence of lymphoid hyperplasia without lymphatic dilatation with mucosal edema (Fig. S1). An antigen-specific lymphocyte stimulation test was only positive for lactoferrin (Table 1). Based on the clinical manifestations and laboratory findings, FPIES was strongly suspected, and an oral test with cow's milk was positive, as the patient experienced frequent projectile vomiting and diarrhea 3 hours after the intake of formula. We confirmed the diagnosis of atypical FPIES.

The clinical symptoms of the patient were characteristic of FPIES, whereas hypoalbuminemia, which was detected at 8 days after the acute onset of FPIES, seemed relatively severe. We considered that PLE with hypoalbuminemia was

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Table 1 Laboratory data

Blood count (day 8)			
WBC	11 700	/μL	
Neutrophils	14.5	%	
Lymphocytes	62.3	%	
Monocytes	17.7	%	
Eosinophils	1.1	%	
Basophils	0.6	%	
Hb	11.8	g/dL	
MCV	76.0	fL	
Platelet	70.9 × 10 ⁴	/μL	
Serum (day 8)			
Total protein	4.1	g/dL	
Na	137	mEq/L	
Cl	106	mEq/L	
Total bilirubin	0.2	mg/dL	
Antinuclear antibody	<×40		
IgA	35	mg/dL	
Albumin	1.6	g/dL	
K	3.7	mEq/L	
Ca	8.6	mg/dL	
CRP	1.15	mg/dL	
IgG	507	mg/dL	
IgM	54	mg/dL	
Infection (day 15)			
Stool antigen test for <i>Helicobacter pylori</i>	Negative		
CMV IgM	<×10		
TB IFN-γ	Negative		
EB-VCA IgM	<×10		
HSV IgM	0.19		
(Cut off, <0.8)			
Urine (day 8)			
Protein	Negative		
Creatinine	95.50	mg/dL	
Protein	24.7	g/dL	
UP/Cr	0.26		
Stool test (day 18)			
Sudan staining	Negative		
Fecal eosinophils	Negative		
Fecal occult blood	Positive		
Allergy test (day 39)			
Total IgE	62	IU/mL	(Standard range 8–56)
TARC	619	pg/mL	(Standard range <1,367)
Immunoassays for allergen specific IgE (day 39)			
Milk	<0.10	IU/mL	Class 0
Wheat	0.48	IU/mL	Class 1
Egg white	2.49	IU/mL	Class 2
Egg yolk	0.37	IU/mL	Class 1
Ovomucoid	<0.10	IU/mL	Class 0
Rice	<0.10	IU/mL	Class 0
Soy	<0.10	IU/mL	Class 0
Casein	<0.10	IU/mL	Class 0
α-Lactalbumin	<0.10	IU/mL	Class 0
β-Lactoglobulin	<0.10	IU/mL	Class 0
Allergen-specific lymphocyte stimulation test [†] (day 39)			
Lactoferrin	Positive	SI: 5.16	(cut off 2.62)
Lactalbumin	Negative	SI: 1.18	(cut off 2.27)
κ casein	Negative	SI: 0.28	(cut off 1.58)

Drug-induced lymphocyte stimulation test [†] (day 202)			
Rotarix®	Negative	SI: 1.2	(cut off 1.6)
α1 antitrypsin clearance test (day 36)	2.9	mL/day	(standard range <13)

CMV IgM, Cytomegalovirus antibody of immunoglobulin M; EB-VCA IgM, Epstein–Barr virus-viral capsid antigen antibody of immunoglobulin M; HSV IgM, Herpes simplex virus antibody of immunoglobulin M; TB IFN-γ, *Mycobacterium tuberculosis*-specific interferon-γ release assay; UP/Cr, urine protein/creatinine ratio.

[†]The allergen-specific lymphocyte stimulation test and drug-induced lymphocyte stimulation test were performed using a liquid scintillation counter (Beta Plate 1205, PerkinElmer Inc. Yokohama, Japan) after the lymphocytes were cultured with ³H-thymidine (PerkinElmer Inc., Waltham, MA, USA).

probably associated with the multiple vaccinations, which were administered 2 days before the acute onset of FPIES (Fig. S2). As rotavirus vaccination is a potential cause of this reaction, we considered it the most probable trigger, as wild-type rotavirus infection can directly cause the onset of PLE in infants.^{3,4} The activation of the immune system by rotavirus may influence structural integrity and vascular permeability, which may play a triggering role in PLE.³ The association of rotavirus infection and food allergy has previously been reported.⁵ Although we did not identify direct evidence linking the rotavirus vaccine and FPIES with PLE in the present patient, careful observation of gastrointestinal complications induced by the rotavirus vaccine is needed for the safe management of infants after multiple vaccinations.

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Disclosure

The authors declare no conflict of interest.

Author contributions

H.N., T.I., and S.K. treated the patient, designed and performed the study, and drafted and revised the manuscript. T.O. and K.I. designed the study, and revised and approved the manuscript. All authors approved the final manuscript as submitted.

References

- Nowak-Węgrzyn A, Chehade M, Groetch ME *et al.* International consensus guidelines for the diagnosis and

- management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J. Allergy Clin. Immunol.* 2017; **139**(4): 1111–26. e4.
- 2 Ntounpara M, Sotiriadou F, Fotoulaki M. Acute-on-chronic food protein-induced enterocolitis syndrome in an exclusively breast-fed infant. *Clin. Case Rep.* 2019; **7**: 71–3.
 - 3 Iwasa T, Matsubayashi N. Protein-losing enteropathy associated with rotavirus infection in an infant. *World J. Gastroenterol.* 2008; **14**(10): 1630–2.
 - 4 Parisi A, Cafarotti A, Salvatore R, Pelliccia P, Breda L, Chiarelli F. Protein-losing enteropathy in an infant with rotavirus infection. *Paediatr. Int. Child Health.* 2018; **38**(2): 154–7.
 - 5 Karakas NM, Arslan A, Atalay E *et al.* May rotavirus vaccine be affect food allergy prevalence? *Hum. Vaccin. Immunother.* 2020; **16**(8): 1952–6.

Supporting Information

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Fig. S1. The histopathological findings. The histology of the duodenum and sigmoid colon by Hematoxylin and eosin (HE) staining. (a) Shortened and widened villi in the duodenum. (Original magnification: $\times 100$). (b) Eosinophils in the duodenum. ($\times 400$). (c) Lymphoid hyperplasia without lymphatic dilatation in the sigmoid colon. ($\times 100$). (d) Eosinophils in the sigmoid colon. ($\times 400$). Mucosal edema and infiltration by lymphocytes and eosinophils were observed (>20 eosinophils in a high-power field), whereas there was no apparent neutrophil infiltration or crypt abscess.

Fig. S2. The hypothesized courses of atypical FPIES in the present case. Hypothesis 1: Chronic FPIES due to cow's milk, which occurred from 2 months of age, caused hypoalbuminemia. Then, gastroenteritis induced by vaccination and fasting triggered acute-on-chronic FPIES at 4 months of age. Hypothesis 2: Vaccination induced gastroenteritis causing acute FPIES and PLE at 4 months of age.