



Clinical Notes

Food protein-induced enterocolitis syndrome caused by egg yolk in an infant

Masaaki Doi,  Yoshitaka Matsubara,  Nayu Iwakoshi and Yasuko Furuichi

Department of Pediatrics, Higashiosaka City Medical Center, Osaka, Japan

Key words egg yolk, food protein-induced enterocolitis, hen's egg, lymphocyte stimulation test.

Food protein-induced enterocolitis (FPIES), non-immunoglobulin (Ig)E-mediated food hypersensitivity, is characterized by repetitive vomiting 3–6 h after ingestion of causative foods. While most common FPIES causative foods include cow's milk and soybeans, hen's egg has been rarely reported (prevalence, 11%).¹ Most reported cases of FPIES due to hen's egg were caused by whole egg or egg white (EW), and only four by egg yolk (EY).^{2,3} Recent *in vitro* studies on FPIES reported on the efficacy of the lymphocyte stimulation test (LST),^{4,5} but its efficacy for EY-caused FPIES remains unclear. Herein, we present a case of EY-caused FPIES in which LST was useful for the diagnostic process. Written informed consent to report this case was obtained from the patient's parents.

A 1-year-old boy had three episodes of repetitive vomiting 90–120 min after ingestion of boiled EY. At the age of 10 months, he presented with vomiting and lethargy 90 min after his first egg intake of 7.5 g boiled EY. Later, he had two similar episodes and was referred to Higashiosaka City Medical Center, Osaka, Japan.

Upon presentation, bodyweight was 10 kg (+0.8 SD), with no eczema or dry skin. Blood tests indicated normal eosinophil count and blood chemistry (Table 1). Serum total IgE and antigen-specific IgE to EW, ovomucoid, and EY were normal, and fecal eosinophils were not detected. Using boiled EY, boiled EW, and allergen reagents (EY, EW; Torii Pharmaceutical, Tokyo, Japan), skin prick and atopy patch tests were negative. Allergen-specific LST (ALST) against EW, ovalbumin, and ovomucoid (BML, Tokyo, Japan) were negative. The LST result for boiled EY (SRL, Toyo, Japan) was considerably higher than those of non-allergic healthy adults; therefore, we judged the result to be positive. Thus, we suspected EY-caused FPIES and conducted oral food challenge (OFC), using 20 g boiled EY. He vomited 90 min after ingestion, and diarrhea was observed twice after >12 h. No other symptoms

were observed. Blood examination concurrent with OFC indicated elevated peripheral neutrophil count and serum C-reactive protein (CRP) and interleukin (IL)-6 (Table 1). One month following EY-OFC, we conducted another OFC using 20 g boiled EW, but no symptoms or serological changes were observed; elevated neutrophil count, however, resulted in a definitive diagnosis of FPIES caused by EY-specific components.

This case provided two crucial clinical suggestions: (i) EY can cause FPIES; and (ii) LST could potentially predict OFC results. First, EY-caused FPIES is extremely rare, with only four reported cases to date.^{2,3} In the present study, EY-OFC was associated with gastrointestinal symptoms and elevated peripheral neutrophil count, and elevated serum IL-6 and CRP. EW-OFC produced elevated peripheral neutrophil count, but no serologic changes or symptoms were observed. Because serological changes reportedly helped in diagnosing FPIES,⁶ we could enhance the diagnostic accuracy of OFC by additional blood tests. The cause of neutrophil elevation in EW-OFC, however, remains unclear; it might be due to contamination of EY antigens.

Second, LST could potentially predict OFC results. Clinician-supervised OFC has broadly been recognized as the only definitive test available.¹ The efficacy of LST for FPIES diagnosis, however, has been recently reported.^{4,5}

In LST, lymphocytes collected from peripheral blood are cultured with allergens and 3H-thymidine; the proliferation of specific T lymphocytes is measured by 3H-thymidine uptake amount.^{4,5} ALST is a more advanced version of the LST and is superior for the following reasons:⁵ (i) antigen management: complete elimination of the non-specific impact of impurities, including lipopolysaccharide, on lymphocyte proliferation; and (ii) establishment of optimal antigen concentration setting and normal values from experiments.

In the present study, EW-LST was carried out using ALST, but EY-LST was carried out using conventional LST in which peripheral blood lymphocytes were cultured with a crude extract of boiled EY. Boiled EY was mixed with 5 mL RPMI 1640 medium supplemented with 20% human AB serum. The supernatant was diluted 50–156 250 times at fivefold increments, and 20 µL was placed in each well of a 96-well culture

Correspondence: Masaaki Doi, MD PhD, Department of Pediatrics, Higashiosaka City Medical Center, 3-4-5, Nishiiwata, Higashiosaka, Osaka 578-8588, Japan.
Email: doi-m@higashiosaka-hosp.jp

Received 25 May 2018; revised 10 October 2018; accepted 6 December 2018.

doi: 10.1111/ped.13785

Table 1 Clinical and laboratory data

Parameter	Patient	Normal
Blood cells (/μL)	11,690	3,500–9,700
Eosinophils (%Leukocytes)	5.0	0–7
Total IgE (IU/mL)	8.0	1–170
TARC (pg/mL)	1,326	<998
Antigen-specific IgE (UA/mL)		
Egg white	0.11	<0.35
Egg yolk	<0.10	<0.35
Ovomucoid	<0.10	<0.35
Skin prick test (wheal/erythema diameter; mm)		
Saline	2×2/4×4	
Histamine dihydrochloride (1.0%)	9×7/21×36	
Egg white reagent	2×2/4×4	
Egg yolk reagent	1×1/3×4	
Boiled egg white	2×2/5×4	
Boiled egg yolk	2×2/5×4	
Atopy patch test		
Egg white reagent	Negative	
Egg yolk reagent	Negative	
Boiled egg white	Negative	
Boiled egg yolk	Negative	

ALST	SI	Maximum reaction (c.p.m.)	CI	Result
Egg white	3.44	773	0.3	Negative
Ovomucoid	1.92	431	0.7	Negative
Ovoalbumin	1.39	313	0.2	Negative
Control	–	225	–	–

LST	Patient	SI	Maximum reaction (c.p.m.)	CI	Result
Boiled egg yolk	18.43	3,522	–	–	Positive
Control	–	191	–	–	–
Five non-allergic healthy adults					
Boiled egg yolk	1.03–1.71	236–928	–	–	Negative
Control	–	136–818	–	–	–

Time (h)	Neutrophils (/μL)	Platelets (×10 ³ /μL)	CRP (mg/dL)	IL-6 (pg/mL)	Histamine (ng/mL)
Egg yolk OFC					
Before	2,587	360	0.01	2.2	0.92
6	7,126	321	0.01	25.6	0.73
24	3,675	366	0.58	1.7	1.05
Egg white OFC					
Before	2,326	534	0.01	1.0	1.61
6	5,297	460	0.01	1.5	1.27
24	2,151	414	0.01	0.8	0.64

ALST, allergen-specific LST; CI, cut-off index; CRP, C-reactive protein; Ig, immunoglobulin; IL, interleukin; LST, lymphocyte stimulation test; OFC, oral food challenge; SI, stimulation index.

plate. Each well then had addition of 200 μL lymphocyte suspension (concentration, 1.0×10^6 cells/mL), and cultured. The highest proliferation of specific T lymphocytes at each concentration ($\times 50$, $\times 250$, $\times 1250$, $\times 6250$, $\times 31250$, $\times 156250$) was then used.

Although EW-LST was negative overall, the EY-LST result was considerably higher than that of non-allergic healthy adults; therefore, we judged the EY-LST result to be positive. The LST results were consistent with OFC results, suggesting that EY- and EW-OFC should be performed to identify the causative agent if the EY-LST is extremely high and EW-LST is negative. Unlike EW-LST, however, EY-LST is not an established test, and its results must be carefully interpreted.

It is unclear which antigen of EY is reacted to. Gal d 5 (α -livetins) and Gal d 6 (YGP-42) have been identified as major EY allergen components that cause an IgE-mediated reaction, but whether these components can cause non-IgE-mediated reactions remains unknown. Currently, no *in vitro* method is available to determine the causative antigen for EY-FPIES; LST using EY components, however, could be a useful method.

In conclusion, this case presents two critical clinical suggestions: EY can cause FPIES; and LST could potentially predict OFC results. Nevertheless, further accumulation of cases is warranted to develop a definitive examination for EY-caused FPIES.

Disclosure

The authors declare no conflict of interest.

Author contributions

M.D. provided medical care and wrote the manuscript; Y.M., N.I., and Y.F. critically reviewed the manuscript. All authors read and approved the final manuscript.

References

- Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: Insights from review of a large referral population. *J. Allergy Clin. Immunol. Pract.* 2013; **1**: 343–9.
- Arik Yilmaz E, Cavkaytar O, Uysal Soyer O, Sackesen C. Egg yolk: An unusual trigger of food protein-induced enterocolitis syndrome. *Pediatr. Allergy Immunol.* 2014; **25**: 296–7.
- Shimomura M, Tanaka H, Meguro T, Kimura M. Three cases of food protein-induced enterocolitis syndrome caused by egg yolk. *Allergol. Int.* 2019; **68**: 110–1.
- Matsumoto K. Non-IgE-related diagnostic methods (LST, patch test). *Chem. Immunol. Allergy* 2015; **101**: 79–86.
- Kimura M, Oh S, Narabayashi S, Taguchi T. Usefulness of lymphocyte stimulation test for the diagnosis of intestinal cow's milk allergy in infants. *Int. Arch. Allergy Immunol.* 2012; **157**: 58–64.
- Kimura M, Ito Y, Shimomura M *et al.* Cytokine profile after oral food challenge in infants with food protein-induced enterocolitis syndrome. *Allergol. Int.* 2017; **66**: 452–7.