

## Acute food protein-induced enterocolitis syndrome due to short-neck clams

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Food protein-induced enterocolitis syndrome (FPIES) is a non-immunoglobulin E (IgE)-mediated food allergy characterized by gastrointestinal (GI) symptoms, including repetitive vomiting and frequent diarrhea. In patients with FPIES, 10–24% have detectable levels of specific IgE (sIgE) against offending foods at presentation or follow-up; patients with concomitant sIgE have atypical FPIES.<sup>1</sup> However, the role of sIgE in FPIES remains unknown. We experienced a rare case of atypical FPIES due to short-neck clams (SNC), in which SNC-induced symptoms persisted even after SNC-sIgE was undetectable.

A 2-year-old girl had recurrent vomiting and pallor without cutaneous, respiratory, neurologic, or circulatory symptoms 2 h after ingesting SNC chowder. Neither bloody stool nor diarrhea was noted. She had several episodes of recurrent vomiting after ingestion of SNC ingredients and scallops, but mollusks, such as squid and octopus, did not elicit any symptoms. The sIgE levels against SNC and scallops were 6.74 kUa/L and 0.85 kUa/L, respectively. At 4 years of age, the sIgE against SNC and scallops was undetectable. An open, oral food challenge test with baked clams was performed by administering an initial dose of five clams (20 g), followed by a second dose of 10 clams (40 g) 1 h later. She had two episodes of vomiting, pallor, and lethargy without cutaneous or respiratory symptoms 2.5 h after the last challenge. The peripheral blood neutrophil count increased from 9,985/ $\mu$ L to 14 400/ $\mu$ L, but the peripheral blood eosinophil count decreased from 129/ $\mu$ L to 0/ $\mu$ L.

To verify the involvement of cell-mediated allergic responses to SNC protein, we conducted a lymphocyte stimulation test and atopy patch test (APT) using the SNC extract, which was prepared by homogenizing raw SNC in phosphate-buffered saline and filtrating supernatants through a 0.20- $\mu$ m-filter after centrifugation. Cell proliferation was evaluated by a Cell Counting Kit-8 (Sigma Aldrich, St Louis, MO). Cytokines in the culture supernatants were measured by BD Cytometric Bead Array (Becton, Dickinson Co., Franklin Lakes, NJ). SNC-specific cell proliferation occurred in the patient's peripheral blood mononuclear cells (PBMCs), but not in those from the healthy controls. The patient's PBMCs produced higher

levels of IL-5, TNF- $\alpha$  and IFN- $\gamma$  in response to SNC extract than those from healthy controls (Fig. 1). No significant difference existed between the patient and healthy controls in IL-4 and IL-10 production by SNC-stimulated PBMCs.

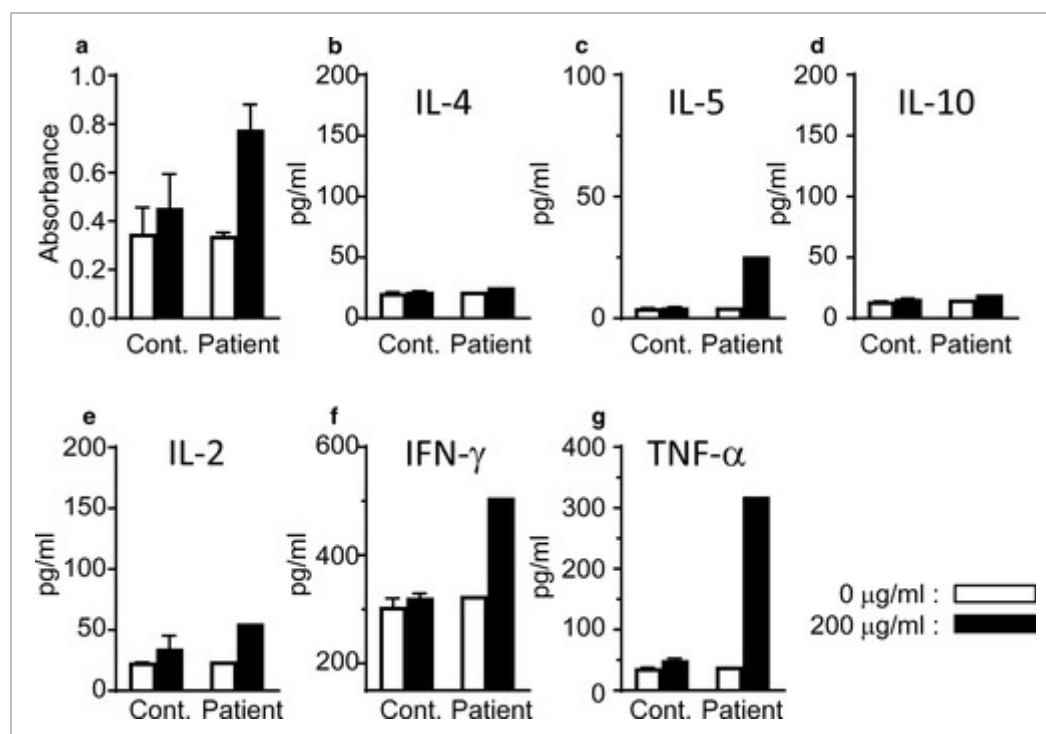


**Fig. 1**

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Antigen-specific lymphocyte proliferation and cytokine production. Peripheral blood mononuclear cells purified from normal controls and the patient were stimulated with 200  $\mu$ g/mL SNC extract for 120 h. (a) Cell proliferation was evaluated by absorbances of the culture supernatants using Cell Counting Kit-8. (b) concentrations of IL-4 (c) IL-5, (d) IL-10 (e) IL-2, (f) IFN- $\gamma$ , and (g) TNF- $\alpha$  in the culture supernatants were measured by BD Cytometric Bead Array.

For the APT, raw SNC extract was applied for 24 h in Finn Chambers (SmartPractice, Japan) on the volar forearm. As a result of skin reactions assessed according to the ICDRG classification,<sup>2</sup> the APT was positive in the patient, but negative in three healthy adult controls without known food allergies.

Our patient met the diagnostic criteria for atypical FPIES proposed by international consensus guidelines.<sup>3</sup> Atypical FPIES is characterized by a small probability of developing tolerance and a potential progression to typical IgE-mediated hypersensitivity,<sup>4</sup> suggesting the possibility of involvement of sIgE in the pathophysiology underlying FPIES. Because FPIES persisted, even without detectable levels of serum sIgE, our case supports the notion that atypical FPIES is heterogeneous and that sIgE was a bystander product in our patient.

Offending foods in FPIES vary geographically, probably based on differences in dietary implementation practices. Seafoods are rarely causative allergens in most countries, except Italy and Spain. FPIES due to clams is very rare, even in these countries.<sup>5</sup>

The antigen-specific lymphoproliferation level was reportedly similar in patients with IgE-mediated cow's milk (CM) allergy and those with GI food allergies. Thus, the SNC-protein-specific lymphoproliferation of the present case indicates the presence of SNC-protein-specific primed T cells, irrespective of the helper activity for SNC-protein-specific IgE production.

Release of the proinflammatory cytokines, TNF- $\alpha$  and IFN- $\gamma$ , by activated PBMCs has been suggested to induce local intestinal inflammation and to increase the intestinal barrier permeability in patients with FPIES. In the present case, SNC-protein-specific IFN- $\gamma$  and TNF- $\alpha$  production, but not IL-4 or IL-10 production, might explain the disappearance of SNC-sIgE and the persistence of GI food allergy to SNC.

The APT's diagnostic value is not well established in FPIES because of its poor sensitivity and utility in predicting tolerance development in FPIES.<sup>6</sup> However, the current patient's positive APT may suggest the presence of SNC-protein-specific T cells, supporting the diagnosis of SNC FPIES.

Although the role of sIgE with respect to the offending food is unclear, this case suggests that sIgE detected in FPIES might vary from a bystander to pathogenic antibodies, depending on the phenotype of atypical FPIES.

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## Disclosure

The authors declare no conflicts of interest.

## Author contributions

H.M. and Y.O. wrote the manuscript and revised the literature. H.M. and T.Y. took part of the PBMC experiment. N.I. and M.M. were involved in atopy patch test. H.M. conceived the case report and Y.O. supervised the draft manuscript. All authors read and approved the final manuscript.

## Informed consent

Written informed consent was obtained from the patient's guardian for publication of this manuscript.

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