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Endoscopic findings in the acute phase of food protein-induced enterocolitis syndromae

To the Editor,

A gastrointestinal (GI) allergy is defined as hypersensitivity reaction of the digestive system after the ingestion of certain foods or drugs. The mildest condition is food protein-induced proctocolitis (FPIPC), which presents as small and fresh rectal bleeding and mucosal edema or erosion of the rectum [1]. The diagnostic guideline for FPIPC includes Odze's pathological criteria: eosinophil infiltration in the colonic lamina propria of ≥ 60 cells/10 high power field (HPF) [2]. However, endoscopic findings in the acute phase of food protein-induced enterocolitis syndrome (FPIES) have not been well documented. We present the first case of a patient with FPIES accompanied by severe diarrhea and hypovolemic shock who underwent sigmoidoscopy on the day of the disease onset.

A girl born on the 36th week of gestation (2350 g) was only fed maternal breast milk. She developed rectal bleeding at 41 days old. As her bowel movements gradually increased, she was seen by a primary care physician. She did not have an ill appearance or weight loss; thus, she received no treatment. However, she gradually developed poor sucking, diarrhea, and body weight loss. She was admitted to the pediatric department of a regional hospital at 56 days after birth. The laboratory data showed an elevated C-reactive protein (CRP) level. A sepsis work-up was performed, and fluid therapy and antibiotic treatment were started. As sepsis due to bacterial transmission from mastitis through breastfeeding was suspected, the patient's mother was instructed to stop breastfeeding and to start bottle-feeding with a cow's milk formula. On the following day, the diarrhea and dehydration worsened, after which hypovolemic shock and seizure started, and she was transferred to our hospital.

Upon admission, she was hypovolemic and acidotic, and she passed whitish watery stool every 10 min. Her white blood cell

count was elevated ($53.6 \times 10^9/l$), CRP level was 8.65 mg/dl, and procalcitonin level was 2.27 ng/ml. There was no peripheral eosinophilia. She required an intravenous fluid infusion (170 ml/kg every 7 h) and a calcium gluconate infusion for hyperkalemia (9.4 mEq/l).

After 3 h of treatment, her vital signs became stable, and sigmoidoscopy without sedation was performed to evaluate the cause of severe diarrhea. The endoscopic findings showed edema and loss of the vascular pattern of the mucosa (Fig. 1). However, erosion and ulcers were not evident. The histopathologic findings from a biopsy specimen of the rectum showed a marked crypt abscess and crypt distortion, which resembled those in ulcerative colitis. Eosinophil infiltration was not observed. Her stool was negative for eosinophils, which was consistent with these findings. Instead, mast cells, which were positive for c-kit immunostaining, were markedly increased (50/HPF) (Fig. 2b). As the blood culture was negative, we suspected that the symptoms were due to FPIES. A lymphocyte stimulation test (LST) against the cow's milk protein showed positive values (stimulation index [SI]: 2.6), and a skin prick testing to the cow's milk also showed a positive result. The patient's serum histamine level increased to 2.58 ng/ml (normal range: 0.15–1.23 ng/ml) upon admission, and her total IgE level was 169.2 IU/l (normal range: <20 IU/l); however, the specific IgEs against the cow's milk, alpha-lactalbumin, beta-lactoglobulin, and casein were negative. The serum cytokine profiles showed a marked elevation of interleukin (IL)-1 beta, IL-6, IL-8, and the tumor necrosis factor (TNF)-alpha, all of which were normalized within 2 weeks after treatment. The IL-4, 5, and 12 were not increased on admission or after treatment. Enteral nutrition with extensively hydrolyzed casein formula was started on the 12th day post-admission without further symptoms.



Figure 1 Endoscopic finding of the sigmoid colon. Marked edema and loss of the vascular pattern of the mucosa are evident.

Sigmoidoscopic findings 3 weeks later showed no remarkable change endoscopically; however, increased eosinophil infiltration (30/HPF) was observed histologically. The casein-specific IgE levels increased 4 weeks later, and the SI in the LST was elevated to 73.3. The milk provocation test resulted in loose stool after drinking 15 ml of cow's milk when she was 1 year and 11 months old.

Food protein-induced enterocolitis syndrome is a non-IgE-mediated GI allergic reaction that predominantly affects infants and children. The clinical presentation of FPIES is primarily vomiting and diarrhea, which can have a sudden onset and rapid progression [3]. The typical course of an acute event is persistent projectile vomiting and pallor followed by diarrhea that can lead to lethargy and dehydration. Symptoms usually resolve within 24–48 h. It is diagnosed clinically after the exclusion of sepsis, metabolic disorders, and anatomic abnormalities. Allergy testing such as specific IgE and skin prick testing is negative in >90% of patients. Neutrophilia and thrombocytosis are reported in >60% of acute cases [4]. At the time of onset, our case had fulfilled the diagnostic criteria for acute FPIES (i.e., persistent vomiting and diarrhea, negative results in the sepsis work-up, and rapid improvement after cow's milk was eliminated from her diet) [5]. Although the total IgE level was

elevated at the time of onset, the specific IgE against cow's milk was not detected, and IgE-mediated signs such as rash, urticaria, and respiratory symptoms were absent. Therefore, we concluded that the initial symptoms were due to a non-IgE-mediated GI allergy (FPIES), not IgE-mediated mechanisms. She only developed an IgE-mediated allergy later, which is often the case with FPIES [5]. Endoscopic findings of the rectum and the colon in patients with FPIES include erosions, erythema, increased hyperplasia, and multiple erosions mimicking infectious colitis in severe cases [6]. However, these findings are only found during the chronic phase of the disease.

Histopathologic examinations of the intestine at different time points in a rat model of food allergy revealed dramatic alterations in the infiltrated cell type at different time points. Mast cells infiltrate the intestinal mucosa within 1 h, induce marked edema of the villi within 3 h, cause eosinophil infiltration within 6 h, increase the goblet cells within 12 h, and cause villous atrophy and lymphocyte infiltration within 24 h [7]. In humans, the endoscopic findings during the very acute phase of FPIES have not been reported. Because eosinophilia is rarely seen in the acute phase of FPIES as was the current case and is often observed in the chronic phase of FPIES, we suspect that mast cell aggregation precedes eosinophil infiltration in FPIES.

In our patient, c-kit-positive mucosal mast cells were markedly increased in the histopathologic findings from a biopsy specimen of the rectum during the acute phase. Mast cells produce several cytokines that modulate the eosinophil biology [8], including growth, differentiation, chemotaxis, survival, and activation. In addition, mast cells synthesize and release TNF- α and IL-2, which promote eosinophil survival, activation, and chemotaxis. Our case also showed an outstanding elevation in the serum IL-2 and TNF- α levels at the time of admission.

Based on these findings, we speculate that mast cells play a role in the development of FPIES during the very acute phase.

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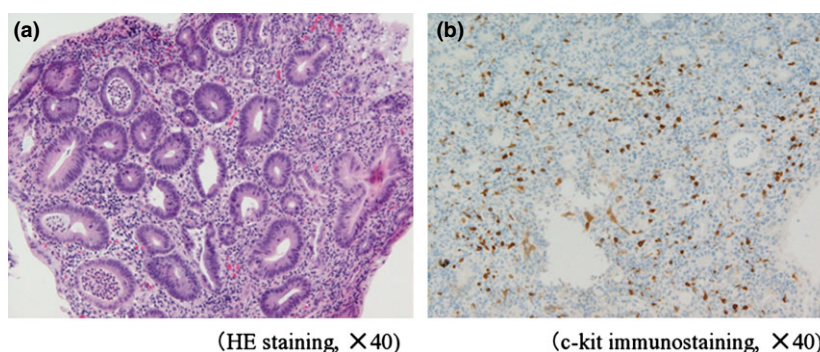


Figure 2 Histopathologic findings of the rectum. (a) Hematoxylin–eosin (HE) staining and (b) c-kit immunostaining. The crypt abscess and crypt distortion are observed. Increased numbers of c-kit-positive cells are noted in the 50/high power field.

(HE staining, $\times 40$)

(c-kit immunostaining, $\times 40$)

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Comment on ‘Anaphylaxis caused by in-season switchover of sublingual immunotherapy formulation’

To the Editor,

As clinicians, we often encounter unpredictable and challenging clinical circumstances that may adversely affect efficacy or safety of a prescribed treatment. Prolonged and unplanned interruption of allergen immunotherapy treatment increases the risk of treatment failure and of adverse reaction on recommencement of treatment (1, 2). In 2013, patients in Australia treated with single-allergen and multi-allergen *Lolium perenne* (*L. perenne*) sublingual immunotherapy (Staloral[®], Stallergenes, SA, France) encountered an unplanned disruption to immunotherapy extract supply at the beginning of *L. perenne* pollen season. The anticipated duration of the supply interruption, which was reportedly due to quality-related manufacturing problems, was at least 2 months. Yalaoui and de Beaumont (3) raised concern regarding the decision to recommend in-season switchover of the immunotherapy formulation to our affected patients but have failed to acknowledge the clinical situation necessitating that measure. Furthermore, such an approach was recommended as an interim therapeutic option by the manufacturer (S. Nicolas, personal communication).

Many Australian patients who had been established on *L. perenne* immunotherapy or who had been commenced on immunotherapy pre-seasonally in 2013 were at risk of treatment failure and significant inconvenience as a result of the unplanned Stallergenes’ immunotherapy extract supply

disruption. To mitigate these risks, we evaluated clinical data in available literature on in-season commencement of immunotherapy in addition to recommendations provided by the local Stallergenes medical team. The decision was to offer our affected patients the option of in-season switchover of sublingual immunotherapy formulation under close specialist supervision. For safety reasons, this optional program was terminated on the first day, after one of two patients developed a severe allergic reaction. Our experience was immediately reported to the Stallergenes medical team and regional colleagues to minimize potential risk to other patients.

We believe that manufacturers and suppliers of allergen immunotherapy extracts need to acknowledge the significant clinical impact of treatment interruption and have a responsibility to ensure that allergen immunotherapy extract supply disruptions are minimized.

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