

Small-bowel capsule endoscopy in patients with gastrointestinal food allergy

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Abstract

Background: Food allergy may present with a plethora of gastrointestinal and extra-intestinal symptoms such as abdominal pain, diarrhea, cardiocirculatory symptoms, cutaneous reactions, or rhinitis. Macropathological lesions like lymphofollicular hyperplasia and erosive or ulcerative lesions have seldom been described in gastroscopy and colonoscopy previously.

Methods: Fifteen patients presenting with unspecific abdominal symptoms in which food allergy was detected in due course were included. During the examination process, those patients showed various indications for small-bowel capsule endoscopy, such as weight loss and anemia.

Results: Fourteen (93.3%) of the 15 small-bowel capsule endoscopies could be assessed, showing nonerosive lesions such as erythema, swelling, and lymphoid hyperplasia in 8 patients (57.1%) and erosive lesions such as aphthoid lesions, erosions, and petechiae in 4 patients (28.6%) with food allergy.

Conclusion: In 15 patients with confirmed food allergy and after exclusion of other diseases, 12 (85.7%) showed various unspecific nonerosive or erosive mucosal lesions within the small bowel, resulting, however, partially in grave consequences such as anemia. Lymphoid hyperplasia was the most prominent finding in 7 patients (50%), albeit infectious disease had been excluded. Anemia improved within 1 year after adequate antiallergic treatment.

Incidence of food allergy has been reported to increase and currently affects 3–5% of the adult population (1–3). It is defined as an immune-mediated hypersensitivity to ingested allergens, whereby mostly IgE-mediated symptoms of type I allergy (Coombs and Gell) occur but also non-IgE-mediated reactions have been described (3–7). Food allergy may present with various clinical patterns, either as acute symptomatology like oral allergy syndrome, acute postprandial rhinitis caused by food allergens (e.g., pollen-associated food allergy), and food-dependent exercise-induced anaphylactic symptoms or as chronic disease like eosinophilic allergic enteropathy, irritable bowel syndrome, or microscopic and allergic colitis (5–11).

Gastrointestinal (GI) food allergy commonly presents with unspecific symptoms like nausea, colicky abdominal pain,

reflux, vomiting, abdominal pain, diarrhea, or hematochezia, whereas extraintestinal signs of allergy such as skin reactions, tachycardia, flush, and urticaria may occur in a lower frequency (2, 8, 10–12). Thus, in patients showing the above-mentioned gastrointestinal symptoms, different diagnostic examinations are conducted, such as transabdominal ultrasound, small-bowel magnetic resonance imaging, endoscopy, and histologic processing, with often unspecific results at best and tissue eosinophilia in only a minority of patients. But until gastrointestinal allergy is diagnosed by demonstration of specific IgE sensitizations in skin, blood, or intestine directing the patients to confirmatory oral provocation tests (single- or double-blind placebo-controlled food challenge), a substantial amount of time is usually passed (6–8, 12, 13).

In literature, macropathological results during gastroscopy and colonoscopy have been mainly described as lymphofollicular hyperplasia, lymphonodular duodenitis or mucosal swelling, erythema, and sometimes erosive lesions like colitis and ulcerative lesions in some patients with gastrointestinal food

Abbreviations

BPCFC, blinded placebo-controlled food challenge tests; CE, capsule endoscopy; GI, gastrointestinal.

allergy (4, 5, 10, 14–16). However, so far, systematic studies investigating the mid-gastrointestinal tract (jejunum, ileum) in food allergy are currently lacking. In this study, we evaluated a small cohort of patients with confirmed gastrointestinal food allergy using wireless capsule endoscopy (CE) for evaluation of the small intestine.

Material and methods

In this study, we included 15 patients with proven gastrointestinal mediated food allergy. All patients presented initially abdominal symptoms, nausea, pain, vomiting, and/or diarrhea after certain meals. Postprandial extraintestinal signs of allergy such as pruritus, flush, bronchial asthma, and allergic rhinoconjunctivitis occurred in 6 of 15 patients (40%).

Before suspicion of gastrointestinal food allergy, an extensive exclusion of various other differential diagnoses (e.g., infections, celiac disease, lymphoma, and neuroendocrine tumor mastocytosis) had already been conducted. Every patient was assessed on grounds of their history and detailed skin prick tests of environmental allergens (molds, fibers, pollen, dust) and food allergens (fish, fruit, vegetables, grains, and different types of wholemeal, flour, bran, egg, milk, meat, soy, spices, and cheese). Carbohydrate malabsorption was known in four patients, but they had persistent symptoms despite avoidance of lactose and fructose. One patient had associated salicylate intolerance, and in two patients histamine intolerance was suspected. In all patients, stool cultures and *Helicobacter pylori* testing were performed with negative findings. Total and antigen-specific serum IgE detections of the putative allergens were performed according to the patients' history or skin tests. Case history, skin test reactions, and serum antigen-specific IgE testing were supplemented in 13 of 15 patients (86.6%) with determination of intestinal antigen-specific IgE during endoscopically guided segmental gut lavage as described previously (11) before performing blinded placebo-controlled food challenge tests (BPCFC). In the case of uncertainties about nontolerated foods, food challenge tests were conducted for basic food-stuff. Confirmatory diagnosis of gastrointestinal food allergy was achieved in nine patients by single-blind and in four patients with double-blind PCFC using a naso-gastric tube (11, 12), while two patients refused to undergo oral provocation because of a history of anaphylactic symptoms.

During the initial clinically indicated work-up, small-bowel CE was performed in these patients because of several symptoms and to exclude other significant pathology of the small bowel. This examination was conducted using Pillcam SB2 (Given Imaging Ltd, Yoqneam, Israel) after overnight fasting and oral ingestion of 2 l PEG solution. The recorded data were searched, documented, and evaluated by two experienced investigators who were blinded to each other's findings. Timing of CE was under an unrestricted diet when patients described episodes of symptoms related to food intake. During the week of CE, no medication was given to any patient. Clinical symptoms, indications for CE, signs of atopy, type of allergic reactions involved, and the main causative food allergens detected during single- or double-blind PCFC are

summarized in Table 1. The study was conducted in accordance with the Helsinki declaration, and all patients gave their informed consent.

Results

Clinical symptoms and indications for capsule endoscopy

Ten of the patients examined were women, and five were men. The mean age was 39.6 years (range, 18–53 years). As illustrated in Table 1, in 12 of 15 patients (80%), clinical signs of atopy were present. Three different pathophysiological allergy types could be identified in this population with nuts, egg, wheat, and milk as the most frequent allergens. Clinical symptoms during unrestricted diet or displayed after specific food challenge during BPCFC included diarrhea (80%), abdominal pain or colics (66.6%), tachycardia (60%), skin reactions (40%), and hypotension (26.6%, Table 1). Endoscopy of the upper and lower gastrointestinal tract was usually performed before CE, and their macroscopic and histologic findings are listed in Table 2. In general, no similarities between CE and endoscopy were found.

Indications for CE were macroscopic or occult gastrointestinal bleeding resulting partly in anemia in 5 of 15 patients (33.3%), weight loss and signs of malabsorption in 6 (40%) patients, suspicion of small-bowel (neuroendocrine) malignancy in 2 (13.3%) patients, or diffuse abdominal pain in 2 patients.

Small-bowel findings in capsule endoscopy

Out of the 15 conducted CEs, 14 could be assessed (93.3%), with one capsule being retained in the stomach.

Among the remaining 14 patients, various pathological findings could be detected in 12 of 14 patients (85.7%). Table 3 lists all pathological findings detected during small-bowel CE. These findings were divided into erosive lesions, nonerosive lesions, findings of unknown functional significance, and clinically irrelevant lesions. Most patients had more than one lesion. Four patients (28.6%) had erosive mucosal lesions, eight patients (57.1%) showed non-erosive lesions, and four patients each (28.6%) had findings of unknown functional significance and/or clinically irrelevant lipid islands, respectively.

Interestingly, 8 of 12 patients (66.6%) showed one or more nonerosive lesions like edema, erythema, swelling, lymphoid follicular hyperplasia, or submucosal lesions in mid-jejunum and ileum (Fig. 1). Lymphoid follicular hyperplasia was the most common pathological finding detected in seven patients (58.3%).

The remaining four patients (33.3%) showed one or more erosive mucosal lesions such as aphthoid lesions, erosions, petechiae, or two inflammatory polyps (Fig. 1). Erosive mucosal lesions were distributed throughout the whole small bowel from duodenum to ileum. Three of those patients with erosive and inflammatory lesions suffered of chronic iron deficiency anemia, despite negative findings during upper or lower endoscopy including negative hemoccult tests before

Table 1 Clinical symptoms, atopy status, indications for capsule endoscopy, and causative allergens identified by blinded placebo-controlled food challenge (BPCFC)

Allergy type	Clinical reactions during food challenge	Eliciting allergens	Indication for capsule endoscopy
Type I allergy (systemic food antigen-specific IgE) <i>n</i> = 9 8 atopics (88.8%) Median serum IgE 168 (84.5–398)	8 diarrhea 4 pruritus, vomiting, abdominal pain, tachycardia 4 epigastric or abdominal pain and colics, bloating 2 nausea, hypotension, GI bleeding, OAS 1 urticaria	6 nuts 3 egg, wheat 3 pollen-associated fruits 1 milk 1 soy flour	3 weight loss, malabsorption 3 macroscopic or occult GI bleeding (anemia) 2 abdominal pain and colics
Type I allergy (local food antigen-specific IgE) <i>n</i> = 2 1 atopics (50%) Median serum IgE 39 (23–77.5)	2 diarrhea 2 abdominal pain 2 iron deficiency anemia	1 milk 1 nuts, pork, egg, wheat	1 iron deficiency anemia 1 exclusion of celiac disease or lymphoma
Suspected type IV allergy (cellular hypersensitivity, no systemic or local food-specific IgE) <i>n</i> = 4 3 atopics (75%) Median serum IgE 68 (12–570.5)	2 diarrhea 2 bloating, vomiting, flatulence, hypotension 1 tachycardia, flush, GI bleeding	2 wheat, beef 2 milk, pork, soy flour, egg	Diarrhea work-up, suspicion of neuroendocrine tumor, GI bleeding

n, Patient number; OAS, oral allergy syndrome.

Atopy status was defined as positive, when history or clinical manifestation of the patient gave evidence for milk crust, atopic dermatitis or eczema, bronchial asthma, and/or allergic rhinoconjunctivitis.

For definition of the allergy type, the most dominant immunologic signs were chosen to classify the ongoing allergic mechanisms.

Type I allergy (systemic IgE sensitization) was recognized when positive skin and/or antigen-specific IgE levels were present in serum (>0.35 U/ml); type I allergy (local IgE sensitization) was diagnosed when intestinal lavage fluid contained elevated food antigen-specific levels of IgE (>0.35 U/mg protein) (11, 12).

Type IV allergy was suspected in four patients who showed markedly increased production of serum TNF levels during or after food challenge, while prechallenge TNF levels were normal during potato–rice diet.

CE. Although after introduction of antigen-specific diet no CE have been conducted, two of three patients with anemia showed an increase in hemoglobin levels within normal range within 1 year of follow-up.

Discussion

Gastrointestinal food allergy has been reported to induce a plethora of clinical symptoms after consuming antigen-containing foodstuffs, but objectification and visualization of corresponding or associated mucosal lesions are difficult (5–7, 9–11, 16–18). Small-bowel CE was not performed directly after antigen-specific oral food challenge procedures, but during an unrestricted diet when patients complained their typical symptoms. Small-bowel CE revealed in 12 of 14 patients (85.7%) various types of mucosal lesions, which were classified as erosive lesions, nonerosive lesions, findings of unknown functional significance, or clinically irrelevant findings. *A priori*, all findings appear to be of unspecific nature, but when considering that all patients had excluded a huge number of differential diagnoses (e.g., infections, celiac disease, inflammatory bowel disease, lymphoma, NSAID intolerance, and malignancy), the high frequency of mucosal lesions in this group of patients with proven gastrointestinal

allergy (2.6 lesions per patient) at a mean age of 39.6 years is surprising. This is even more surprising when compared to existing studies, in which patients of a comparable age (34.5 and 43 years, respectively) presenting with chronic abdominal pain and negative endoscopic and radiological examinations but without common underlying disease (19, 20). In these groups, pathological findings were detected in up to 43%.

Nonerosive and other unspecific inflammatory changes like edema, swelling, and erythema were found as most frequent findings in gastrointestinally mediated allergy, but such lesions usually require above-mentioned differential diagnosis. As such diseases have been excluded in all patients, these unspecific nonerosive mucosal lesions demonstrate that intestinal mucosal physiology may become altered in food allergy and they reflect probably (subtle) intestinal allergic manifestations as has been reported from other investigators at other anatomic sites (7, 16–18). Although of unspecific nature, some of these mucosal features may be responsible for certain clinical and functional symptoms of patients with gastrointestinal allergy as dysmotility, bloating, heat sensations, or increased intestinal secretion. Delayed capsule excretion occurred in two of three patients with typical nonerosive lesions like mucosal swelling, edema, or lymphofollicular

Table 2 Endoscopic and histologic findings in 15 patients with GI food allergy at the upper, mid and lower GI tract

Patient no.	Esophago-gastro-duodenoscopy	Histology – upper GI tract	Capsule endoscopy	Ileo-colonoscopy	Histology – lower GI tract
1	Normal	Normal	Nonerosive lesions	Normal	Normal, exclusion IBD
2	Chronic erosions	<i>Helicobacter pylori</i> -neg. chronic gastritis	Nonerosive lesions, delayed capsule excretion	Hyperplastic polyp, patchy erythema, hemorrhoids	Hyperplastic polyp, normal
3	Fundic glands atrophy antrum	Normal	Nonerosive lesions	Hypertrophic anal papillae	LH ileum, edema, and mild tissue eosinophilia
4	Nonerosive reflux lesions at cardia, erythema corpus	<i>H. pylori</i> -neg. chronic gastritis	Erosive lesions	LH, patchy erythematous colonic lesions, rectal tubular adenoma	LH, tubular adenoma
5	Normal	Normal	Normal	Normal	Normal
6	Axial hiatal hernia and nonerosive esophageal reflux lesions	NERD, chronic type C gastritis	Erosive lesions	Cecum erythema hyperplastic rectal polyps (<5 mm)	Normal ileum, mild eosinophilia right hemicolon, hyperplastic polyps
7	Normal	Normal	Nonerosive lesions, lipid islets jejunum	Normal	Normal
8	Atrophy antrum and duodenum	Normal	Normal	Normal	Patchy edematous colonic mucosa
9	Aphthous lesions antrum, chronic erosions	Acute and chronic pangastritis with lymphocyte proliferation	Erosive lesions, lipid islets duodenum	4 colorectal adenoma (2–14 mm)	2 tubular and 2 tubulovillous adenoma
10	Ectopic pancreas antrum 2 acute erosions duodenal bulb	<i>H. pylori</i> -neg. chronic corpus gastritis	Nonerosive lesions, lipid islets jejunum, delayed capsule retention	Normal	Lipid islets ileum, edema ileocecal valve
11	Erosive esophageal reflux	Gastroesophageal reflux disease with suspected short-segment Barrett mucosa	Nonerosive lesions	Normal	Normal
12	Atrophy antrum, bile reflux at pylorus	Atrophy and intestinal metaplasia	Nonerosive lesions, lipid islets duodenum	Hyperplastic polyps rectum	Hyperplastic polyps rectum
13	Chronic erosions, erythema, stomach and duodenum, suspected unspecific duodenitis	Acute gastritis, increased lymphocyte numbers in duodenum, exclusion IBD celiac disease and Behcet's disease	Erosive lesions, delayed capsule excretion	Normal	Normal, exclusion IBD
14	Acute and chronic stomach erosions, ectopic gastric mucosa duodenum	Chronic type C gastritis	Capsule retention stomach	Hemorrhoids	Normal
15	Nonerosive reflux at cardia	Edema at cardia and mild eosinophilia	Nonerosive lesions	Isolated colonic ulcer at ileocecal valve (6 mm)	Benign ulcer with surrounding mild tissue eosinophilia, suspected NSAID lesion

GI, gastrointestinal; IBD, inflammatory bowel disease; neg., negative; LH, lymphofollicular hyperplasia; NERD, nonerosive gastroesophageal reflux disease, NSAID, nonsteroidal anti-inflammatory drugs.

Endoscopic and histologic results from upper and lower gastrointestinal tract were compared with capsule endoscopy findings. Some patients had more than one qualitative pathological finding during endoscopies.

Table 3 Findings during capsule endoscopy (CE) in 15 patients with gastrointestinal food allergy

	Frequency of findings	<i>n</i>	Locations of findings		
			Duodenum	Jejunum	Ileum
Nonerosive lesions	Lymphoid follicular hyperplasia	7		2	5
	Edema, swelling	4		2	2
	Erythema	3	2		1
	Submucosal lesions	3		1	2
	Focal lymphangiectasia	2	1	1	
	Relative stenosis	2		1	1
	Sum of all types of nonerosive lesions	21	3	7	11
8 patients					
Erosive lesions	Aphthoid lesions	3	1	1	1
	Erosions	3	2	1	
	Petechiae	2		1	1
	Inflammatory polyps	2	1	1	
4 patients	Sum of all types of erosive lesions	10	4	4	2
Not relevant findings	Lipid islands	4		2	2
4 patients					
Findings of unknown functional significance	Capsule retention in stomach (swelling?)	1			
4 patients	Delayed capsule excretion	3			

The patient numbers of nonerosive or erosive lesions, findings of unknown functional significance, or clinically irrelevant findings during CE are given in Table 3 for the whole group and according to their locations within the small bowel. *n* represents the number of findings, with some patients showing more than one qualitative pathological finding.

In 8 patients, a total of 21 nonerosive lesions were found (3 per patient), with predominant location at jejunum and ileum.

In 4 patients with erosive lesions, a total of 10 erosive lesions (2.5 per patient) were found with predominant location at proximal parts of the small bowel.

hyperplasia. Thus, it might be speculated whether these nonerosive lesions contribute to motility complaints, altered small-bowel function with reduced emptying of intestinal contents to the colon, or abdominal heat sensation in food-allergic individuals. Interestingly, in one patient with the above-listed symptomatology, nonerosive swelling was accompanied by extreme edema of the ileocecal valve (12 mm), which could also be observed during ileo-colonoscopy as an extremely rare event. But among the eight patients with nonerosive small-bowel lesions, ileo-colonoscopy was normal or inconclusive in at least five of eight patients. Thus, CE should be performed after inconclusive ileo-colonoscopy, and its clinical value is to supplement usual gastrointestinal diagnostics regarding the presence of small-bowel pathology. Unfortunately, at present, CE is not able to take biopsies for histology, but in patients with nonerosive mucosal lesions of the small bowel, performance of modern enteroscopy (e.g., double-balloon enteroscopy) should be discussed for further histologic assessment, measurement of food-specific intestinal IgE, or local food challenge within the jejunum. Topographically, nonerosive lesions were more often located in distal small-bowel segments (ileum), while erosive lesions were found in duodenum and proximal jejunum (Table 3).

Interestingly, lymphofollicular hyperplasia, which has also been described by several other investigators at the upper (duodenum) or lower gastrointestinal tract (ileum, cecum, colon ascendens), was the most prominent finding during small-bowel CE in our allergic patient cohort, albeit enteric infections or *Helicobacter* gastritis had been carefully

excluded (4, 5, 15). So far, only one radiological study using enteroclysis was conducted to inspect larger parts of the small intestine in gastrointestinal allergy, but because of the more luminal orientation and their (sub)-mucosal location, conventional radiology failed to detect the increased occurrence of lymphoid follicles in this condition (3–5).

Erosive mucosal lesions were detected in a minor frequency, but may explain positive hemocult tests and iron deficiency anemia in gastrointestinal allergy as has been reported in children and adults as a rare complication of food allergy (15–17) and may resolve after adequate antiallergic treatment (16). As has been shown in our cohort, 3 of 15 patients (20%) with normal or inconspicuous findings at upper or lower gastrointestinal endoscopy suffering from anemia caused by occult gastrointestinal blood loss had unexpected erosive or inflammatory lesions of the small bowel at the time of CE, and they recovered their hemoglobin levels within 1 year after allergen-specific avoidance. Thus, in contrast to conventional radiology, wireless small-bowel CE helps to visualize minute mucosal lesions in patients with gastrointestinal allergy and identifies the causes of otherwise unexplained anemia in certain allergic individuals as erosive, inflammatory, or ulcerative mucosal lesions. It demonstrates further that mucosal integrity in gastrointestinal allergy may become altered, manifesting with erosions or, in more severe cases, with ulcers (16, 17).

The reason for erosive and nonerosive lesions in patients with food allergy is partially the ingestion of food antigens triggering the development of an acute local anaphylactic

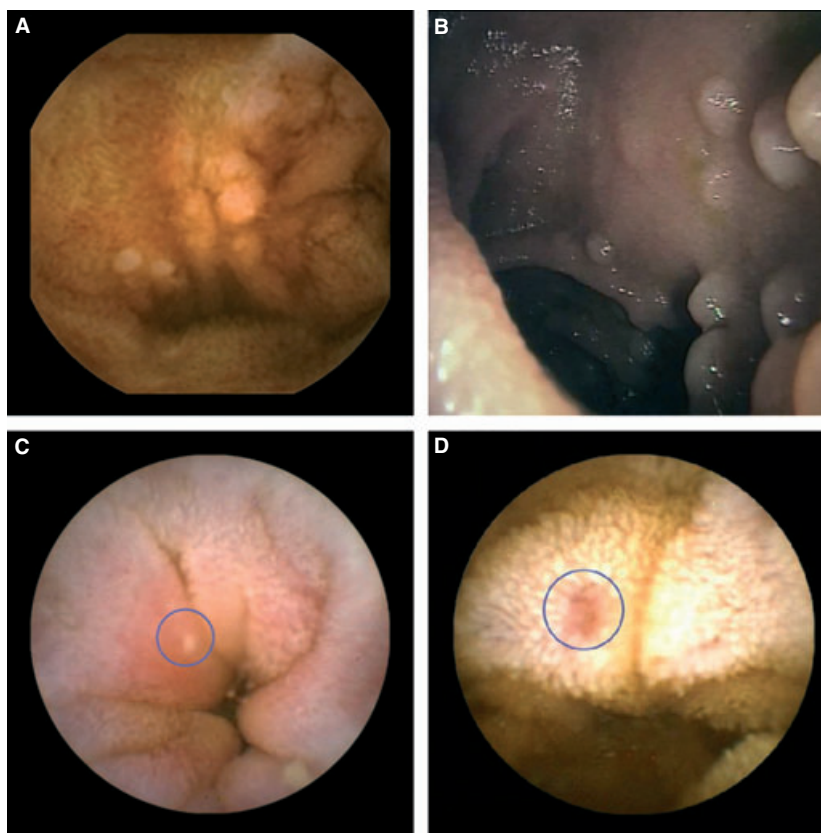


Figure 1 (A and B) Lymphofollicular hyperplasia in capsule endoscopy and endoscopically. These are common in patients with gastrointestinal mediated food allergy. Aphthoid lesions (C) and acute erosion (D) are also regularly found in patients with other

diseases such as gastrointestinal bleeding and Crohn's disease. These lesions can lead to chronic anemia caused by intermittent blood loss in gastrointestinal food allergy.

inflammatory reaction (17), with production of short- or long-living mediators. While histamine and eicosanoids, for instance, may be responsible for the induction of observed nonerosive lesions, longer-acting mediators like cytokines, mast cell tryptase, or cationic proteins are suspected to be involved in erosive lesions, resulting in further alterations of the mucosal barrier and the lymphatic cell population (11, 15–18).

Thus, in summary, wireless CE detected a high frequency of various nonspecific mucosal lesions in the small bowel of patients with known gastrointestinal allergy. It is concluded that nonerosive, erosive, and lymphonodular lesions within the jejunum and ileum are an important morphologic feature of intestinal allergic inflammation and mucosal immune system activation, which may explain, at least in part, some

gastrointestinal, functional, neurovegetative, and subjective symptoms in patients with food allergy.

Author contributions

All the authors contributed to the work in substantial matters, such as conception and design of study, acquisition of data, and interpretation of data, significantly involved in drafting the article or revising it critically for important intellectual content, and approved the final version to be published.

Conflict of interest

The authors declare that they have no competing interests.

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