

BRIEF COMMUNICATION

Food Hypersensitivity as a Cause of Rectal Bleeding in Adults

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Background & Aims: Rectal bleeding and lymphonodular hyperplasia (LNH) in children can be caused by food hypersensitivity (FH). Our aim was to verify whether similar clinical and endoscopy presentations in adults can be due to FH. **Methods:** Consecutive adult patients with rectal bleeding were enrolled. All underwent routine assays, colonoscopy, and histology study. **Results:** Ten of 64 (15%) patients showed LNH as the unique sign at colonoscopy. An oligoantigenic diet resolved the rectal bleeding in 9 patients, and the reintroduction of several foods caused symptom reappearance. Double-blind placebo-controlled challenges with cow's milk and wheat protein confirmed the FH; symptoms reappeared 1–96 hours after the challenge. None of the patients were positive for IgE-mediated assays. In patients with LNH and FH, histology of the ileum and colon mucosa showed a higher number of lymphoid follicles and intraepithelial and lamina propria eosinophils compared with the other patients with rectal bleeding. **Conclusions:** Recurrent rectal bleeding can be caused by FH in adult patients. Endoscopic evidence of LNH characterizes these cases.

Rectal bleeding caused by allergic proctitis is a clinical manifestation of food hypersensitivity (FH) in infants.^{1,2} However, in a recent article we showed that rectal bleeding related to a condition of FH can occur also in school-age children.³ In these older children the main endoscopic characteristic was the presence of lymphonodular hyperplasia (LNH) of the colon and/or the ileum.³ Others described LNH as an endoscopic marker of cow's milk allergy in children.^{4–8}

This prospective study showed that rectal bleeding and intestinal LNH can be caused by FH in adult patients.

Patients and Methods

Consecutive patients with rectal bleeding and referred to our Institute between January and December 2005 were enrolled. Rectal bleeding was defined as evacuation of blood alone or of unformed stools mixed with blood.

Inclusion criterion was a history of recurrent rectal bleeding lasting more than 3 months, with a frequency ≥ 1 episode per week. Exclusion criteria were (1) treatment with steroids or an exclusion diet for whatever reason and (2) presence of concomitant symptoms or laboratory results suggesting an inflammatory bowel disease.

Routine biochemistry and allergology tests were performed as described.^{9,10}

Endoscopy and Histology

Colonoscopies were performed as far as the terminal ileum. Any endoscopic abnormalities were noted and recorded for off-line reappraisal. LNH was defined as a cluster of ≥ 10 extruding lymphoid nodules as previously described.³ Biopsies were taken from the terminal ileum, from each segment of the colon, and from areas where endoscopic lesions were noted. Histologic examination was performed by a pathologist unaware of the clinical and laboratory data of the patients. Intraepithelial and lamina propria eosinophils and lymphocytes were counted.^{9,11}

Other Investigations

The diagnostic work-up could have included screening for celiac disease, serum immunoglobulin, stool examination and culture, serum anti-human immunodeficiency virus antibodies, chest radiography, esophagogastroduodenoscopy with biopsy, small-bowel follow-through study, abdominal ultrasonography, and computed tomography scan. The patients were followed up for a median of 25 months to confirm the diagnoses.

Evaluation of the Relationship Between Lymphonodular Hyperplasia and Food Hypersensitivity

To assess a possible relationship between LNH, rectal bleeding, and FH, all patients with LNH as the sole abnormality and without a definitive diagnosis commenced an oligoantigenic diet containing rice, lamb, carrots, olive oil, salt, and sugar. After 4 weeks, the subjects remaining asymptomatic on this regimen were introduced to new foods singly, with at least 8 days between the introduction of each new food. Tolerated foods were kept in the diet. After the introduction of a new food if the patients observed the reappearance of rectal bleeding, this food was excluded from the diet. If the symptom disappeared again, a second challenge was performed after at least 2 months to confirm FH. The first challenge was performed at home in an open fashion. The second challenge was performed at home by using the double-blind pla-

Abbreviations used in this paper: DCPC, double-blind placebo-controlled; FH, food hypersensitivity; LNH, lymphonodular hyperplasia.

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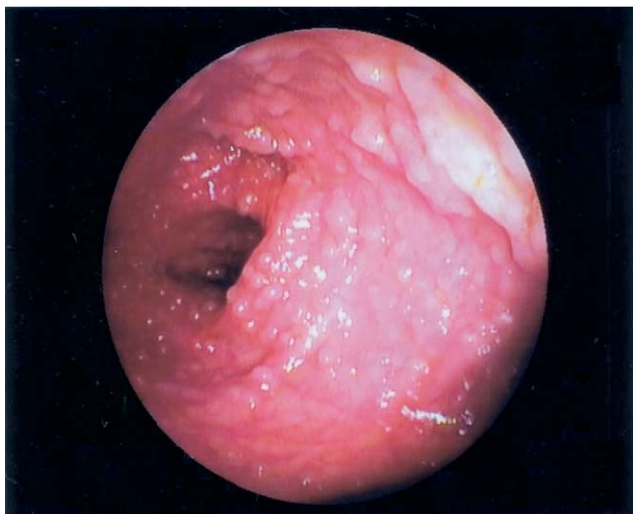


Figure 1. Colonoscopic finding showing dense LNH in the left colon.

cebo-controlled (DBPC) method for cow's milk and wheat.¹¹ DBPC for cow's milk was performed by administering capsules coded as A or B containing milk proteins or xylose, respectively. DBPC for wheat proteins was performed with capsules containing wheat or xylose. Capsules A or B were given for 2 consecutive weeks, and then after 1 week of washout, the patients received the other capsules for 2 weeks. The challenge was stopped when a clinical reaction occurred. The patients wrote a dietary diary, and the adherence to the elimination diet was evaluated by trained dietitians. Hypersensitivity to other foods (soy, tomatoes, etc) was only tested at home in an open fashion.

The patients gave their written consent to the study. The protocol was approved by the Ethics Committee of the University Hospital of Palermo.

Frequency analysis was performed with the Fisher test. Student *t* test or Bonferroni test was used for means comparison.

Results

A total of 98 patients with rectal bleeding were evaluated. Thirty-four were excluded because clinical and/or laboratory data indicated an inflammatory bowel disease. Sixty-four patients (me-

dian age, 40.5 years; range, 18–79 years; 34 male/30 female) completed the study. The final diagnoses in these patients were hemorrhoids (N = 20), anal fissures (N = 5), large tubular adenoma (N = 10), large villous adenoma (N = 6), colon carcinoma (N = 5), angiodysplasia of the colon (N = 2), ulcerative proctitis (N = 6), and LNH (N = 10). LNH was in the terminal loop of the ileum and in the rectum in 4 patients, in the terminal ileum, colon, and rectum in 5, and exclusively in the terminal ileum in 1 (Figure 1). All these patients exhibited erythema and edema of the rectal mucosa, with presence of bright red blood after endoscope touching.

Patients with LNH underwent a complete work-up; none were positive for celiac disease-specific antibodies (anti-tissue transglutaminase and endomysial antibody) and had a reduction in the villi/crypts ratio in the duodenal mucosa. All other differential diagnoses were excluded.

All patients with LNH received the above described oligoantigenic diet for 4 weeks. During this period 9 patients remained asymptomatic. In these 9 patients, subsequent open challenge determined the reappearance of rectal bleeding associated with abdominal pain and bowel habit change (Table 1).

The subsequent DBPC challenge determined the reappearance of rectal bleeding, abdominal pain, and bowel habit change but did not show any symptoms when the 9 patients assumed placebo.

The patients with rectal bleeding caused by FH were younger than the other 54 included in the study (28 ± 10 versus 58 ± 21 years; *P* < .0001), exhibited a higher frequency of self-reported food intolerance (5 of 9 versus 3 of 54; *P* = .02), and had undergone a higher number of previous endoscopic examinations (between 2 and 4 colonoscopies) (*P* = .04); there was no difference as regards the duration of the symptoms (4.2 ± 1.9 versus 2.3 ± 9.3 years). The immunologic assays did not show positive IgE-mediated assays (radioallergosorbents, prick tests) in the FH patients. Five patients were positive for serum IgG anti-gliadin antibodies and underwent HLA determination, although they had a normal duodenal histology. Only one of these was positive for DQ2 or DQ8 haplotypes.

The histology showed that FH patients had a higher number of lymphoid follicles and intraepithelial and lamina propria eosinophils than the other patients studied in the ileum and in each segment of the colon-rectum. No patients exhibited histologic features suggestive of inflammatory bowel disease.

Table 1. List of Foods That Caused Symptom Reappearance at the Time of the Open Challenge, Time of the Reaction After Food Assumption, and Kind of Symptoms Reappearing in 9 Patients Who Were Asymptomatic on Oligoantigenic Diet

Patient no.	Food causing symptoms	Time of the reaction (h)	Symptoms at the challenge
1	Cow's milk, wheat, eggs, tomatoes, cocoa, beef, legumes, soy, oranges, fish, peas, cauliflowers, bananas	1	Rectal bleeding, abdominal pain, diarrhea
2	Cow's milk, wheat, eggs, tomatoes, cocoa, beef, legumes, soy, oranges, fish, peas, cauliflowers	48	Rectal bleeding, abdominal pain, diarrhea
3	Cow's milk, wheat, eggs, tomatoes, cocoa, beef, legumes, soy, oranges, fish	4	Rectal bleeding, abdominal pain, diarrhea
4	Cow's milk, wheat, eggs, tomatoes, cocoa, beef, legumes, soy, oranges	96	Rectal bleeding, abdominal pain, constipation
5	Cow's milk, wheat, eggs, tomatoes, cocoa, beef, legumes	1	Rectal bleeding, abdominal pain
6	Cow's milk, wheat, eggs, tomatoes, cocoa	24	Rectal bleeding, abdominal pain, diarrhea
7	Cow's milk, wheat	6	Rectal bleeding, abdominal pain
8	Cow's milk, wheat	1	Rectal bleeding, abdominal pain, diarrhea
9	Cow's milk, wheat	1	Rectal bleeding, abdominal pain

During follow-up the patients with FH continued to follow an elimination diet with the exclusion of the foods that caused rectal bleeding, and none experienced new episodes. Occasional ingestion of the eliminated foods always caused the recurrence of the rectal bleeding associated with abdominal pain. After 12–15 months all these patients underwent a second colonoscopy; the recordings of the endoscopy examinations showed a reduction in the number and size of the LNH clusters.

Discussion

Allergic proctitis is a quite common manifestation in infants with cow's milk allergy.^{1,2} Furthermore, it can occur in school-age children,^{3,5,12} who frequently exhibited LNH of the colon, which is now considered a possible marker of FH in children.^{3–8} On this basis, we performed a study in adults to search for a possible relation between FH, proctitis, and LNH.

Although LNH can be due to several causes,^{13–15} our study showed that LNH not associated with other endoscopic signs is often due to FH in adults. The most important finding of our study was the high frequency of FH as cause of recurrent rectal bleeding; 9 of 64 patients (14%) with rectal bleeding had a final diagnosis of multiple FH. It must be underlined that this quite high frequency could be not universally representative of the subjects with rectal bleeding because our center has a well-known history of interest in FH, and this could have determined a selection bias.

The diagnosis of FH in the patients included in the prospective study was based on rigorous criteria¹⁶: a DBPC challenge with cow's milk and wheat. The clinical history of the allergic patients showed that abdominal pain and bowel habit disturbances very often accompanied the rectal bleeding. All these patients had undergone multiple investigations in the past (a mean of >2 colonoscopies), but no diagnosis had been made. However, the patients themselves had often reported FH, but this was not taken into consideration by the clinicians who treated them. It is probable that the negative IgE-mediated assays in these patients had contributed to a misdiagnosis, but previous articles on children with FH and endoscopic evidence of LNH showed that the skin prick test and food-specific IgE antibodies were negative.^{9,17} Consequently, although gastroenterology manifestations of FH in adults are considered rare,^{18,19} we suggest that a higher level of suspicion with more frequent recourse to the elimination diet and DBPC challenge could evidence a higher frequency of FH diagnoses.

The mucosa histology of the adults with LNH and FH strongly confirmed the data observed in children with the same clinical picture; there was an increase in the number of intraepithelial and of the lamina propria eosinophils^{3,9} and in the number of lymphoid follicles.²⁰

The aspect of the rectal mucosa (erythema, bleeding after touching) suggests that proctitis is always present in these patients, and we suggest the rectal mucosa as the source of bleeding, with mechanisms similar to the picture of food-induced proctocolitis in infancy.^{1,2} LNH is not the source of bleeding; in fact, in other patients with rectal bleeding referred to our institution out of time of this study, we made a diagnosis of FH, although they did not exhibit LNH of the colon or the ileum.

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