

Dietary Protein-Induced Proctocolitis in Childhood

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Cow's milk protein-induced proctocolitis presents with overt rectal bleeding in otherwise healthy infants and is characterized by an eosinophilic infiltrate of the left colonic mucosa. Although it is the most common cause of proctocolitis in infancy, dietary protein-induced proctocolitis had hardly ever been reported in childhood so far. We hereby report 16 otherwise healthy children aged 2–14 yr, who presented over a 6-yr period with persistent or recurrent rectal bleeding related to a mild form of left-sided colitis characterized by a prominent eosinophilic infiltration, focal lymphoid follicle hyperplasia, and a prompt clinical and histological response to a cow's milk-free diet. No patient had a history of food-induced proctocolitis during infancy, and most patients did not show an IgE-mediated response to cow's milk protein. Half of the patients did have other gastrointestinal symptoms, but no systemic symptoms were present and other causes of colitis were excluded by appropriate investigation. Tolerance to cow's milk protein developed in half of the patients within a year. Dietary protein-induced proctocolitis is a relatively common cause of overt rectal bleeding in childhood, and its features are remarkably similar to those of dietary protein-induced proctocolitis of infancy.

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INTRODUCTION

Dietary protein-induced proctocolitis—also known as allergic eosinophilic proctocolitis—is characterized by the passage of bloody and sometimes mucousy stools in otherwise healthy, often breast-fed infants (1–3), in whom rectal and colonic biopsies show a significant eosinophilic infiltration of the lamina propria as the most prominent feature (4–6). Exclusion of cow's milk protein from the baby's formula or from the lactating mother's diet is followed by prompt clinical remission, and tolerance to cow's milk is usually acquired within a year (1–6, 7). A few cases related to intolerance to hydrolysate formula, soy-based formula, or other dietary proteins from the mother's diet have also been described (1, 8, 9). Dietary protein-induced proctocolitis is mostly a non-IgE associated disease where a T-cell-mediated reaction to cow's milk protein has been suggested as the putative underlying mechanism (10). Although dietary protein-induced proctocolitis is relatively common in infancy (11), only very few suspected and poorly defined cases have been reported in children so far (12).

CASE REPORTS

Our unit is based in a large regional hospital located in a highly industrialized area and serving a population of about 2,000,000. It is a major regional referral center for pediatric GI disorders, with a major interest in motility disorders, functional disorders, inflammatory bowel disease, and food hypersensitivity including celiac disease.

Over the last 6-yr period, in our unit we have made a definitive diagnosis of dietary protein-induced proctocolitis in 16 children aged 2–14 yr (mean 7.5 yr), who—like the infants with the same disorder—presented with rectal bleeding as the major and often only clinical symptom. All these patients responded to a cow's milk-free diet and relapsed upon open challenge with cow's milk, and in all patients endoscopic biopsies showed a greater number of eosinophils in the lamina propria of the rectum, sigmoid, and colonic mucosa. Other conditions possibly causing rectal bleeding such as bacterial and parasitic infection, inflammatory bowel disease, vascular malformation, intestinal polyps, etc., were excluded by clinical history, thorough clinical examination, colonoscopy and colonic histology, and other appropriate investigation on stools and serum.

Over the same time period, 96 other pediatric patients were referred to our unit because of persistent or recurrent rectal bleeding, and in these patients the definitive diagnosis was the following: 31 chronic constipation with anal fissures, 28 inflammatory bowel disease (16 Crohn's disease, 11 ulcerative colitis, 1 indeterminate colitis), 20 allergic eosinophilic proctocolitis of infancy, 7 infectious colitis, 4 unexplained (no causes found), 3 juvenile polyps, 1 solitary rectal ulcer, 1 rectal angiodysplasia, 1 Heiner's syndrome. Therefore, in our setting allergic eosinophilic proctocolitis caused 18% of all cases of overt rectal bleeding in infants and children, a percentage similar to that of Crohn's disease and second only to anal fissures due to chronic constipation.

All patients had been referred to our outpatients' clinic by a general pediatrician for the first evaluation of rectal

bleeding, and in none of them food allergy had been previously suspected as a cause of the bleeding.

The most relevant demographic and clinical features of these 16 patients are summarized in Table 1 and are described in detail below.

Rectal Bleeding

In all patients streaks of bright red blood—often but not always mixed with mucus—were clearly visible in the stools and/or in the toilet. In four patients the amount of blood was occasionally reported to splash in the toilet during defecation. In different patients the frequency of rectal bleeding varied from daily to once every two weeks, with a mean of twice weekly. Two patients who also had diarrhea (see below) were reported as having occasional bloody diarrhea, *i.e.*, loose stools mixed with small amounts of bright red blood and mucus. In all patients, rectal bleeding was the symptom that prompted the request for a gastroenterologist's evaluation.

Other Gastrointestinal (GI) Manifestations

Nine of 16 patients had other gastrointestinal GI manifestations such as abdominal pain (4), nausea and/or regurgitation or vomiting (4), diarrhea (2), anal fissure (2), hematemesis (1), and recurrent aphthous stomatitis (1).

All these manifestations were reported as occasional or sporadic and had not led to specialist evaluation or specific investigation. Anal fissures were reported in the past history by two patients, but were not present at the time of examination and these two patients were not constipated. Abdominal pain, nausea, and vomiting were reportedly unrelated to the meals and to bowel movements. One patient with occasional vomiting and hematemesis had been previously diagnosed elsewhere as having gastroesophageal reflux disease, and had been treated unsuccessfully with proton pump inhibitors. No patients reported systemic or organ symptoms such as fever, joint pain/swelling, liver enlargement, jaundice, unexplained skin rash, etc. Growth was reported as normal in all patients, whose weight and height charts were reviewed for an objective assessment of their growth pattern, which in fact resulted normal.

Symptom Onset and Duration

In 13 out of 16 (81%) patients, rectal bleeding had begun during primary school age and in all patients rectal bleeding had been continuing for 1 month to 4 yr (mean 11 months) at the time of our first visit. None of our patients reported a history of previous rectal bleeding during infancy.

History of Atopy

Four of 16 patients had a personal history of previous and/or concurrent nongastrointestinal allergic disease: 3 suffered from asthma (one of them also had rhinitis) related to such aeroallergens as dust mites, grass pollen, birch pollen and cat/dog dander, and 2—including one with asthma—had suffered from atopic dermatitis due to cow's milk allergy during infancy. Furthermore, 2 other patients had a family history

of atopy, *i.e.*, asthma and urticaria in the mother. In these patients, a positive personal or family history of atopy was not significantly more common than in patients with rectal bleeding due to other GI disorders such as IBD and anal fissures.

Evidence of IgE-Mediated Hypersensitivity

All the patients were tested for total (PRIST) and specific (RAST) IgE levels to common food antigens including cow's milk, egg, wheat, fish, tomato, soy, nuts, and peanut. Three of 16 (19%) had a laboratory evidence of an IgE-mediated response to multiple food antigens, namely cow's milk and egg (two) and cow's milk, egg and wheat (one). Two of these 3 also had high levels (474 and 2,103 KU/L, respectively) of total IgE. Also the frequency of positive PRIST or RAST in these patients was not significantly different from that of patients with rectal bleeding due to IBD and anal fissures.

Laboratory Investigation

All patients underwent serological tests including full blood count, serum iron and ferritin, ESR, CRP, immunoglobulin, total serum protein and electrophoresis, liver function tests, prothrombin and partial thromboplastin time, fibrinogen, and urinalysis. With the exception of two cases of mild microcytic anemia (with Hb values of 10.5 and 9.8 g/dL, and MCV values of 72 and 62 μ^3 , respectively), all these tests gave entirely normal results. Peripheral eosinophilia ranging from 6.1% to 10.1% of total WBC count was seen in 33% of patients. Antibodies directed to the cytoplasm of neutrophil granulocytes (p-ANCA) and to the yeast *Saccharomyces cerevisiae* (ASCA) were also tested by ELISA and immunofluorescence in all patients, with negative results. Stool culture for major enteric pathogens including *Salmonella typhi*, *Shigella dysenteriae*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *Enteroinvasive* or *Enterohemorrhagic E. coli* and *Clostridium difficile*, and stool examination for ova and parasites were also carried out and tested negative in all patients. Four patients—two with diarrhea and/or anemia and one with recurrent mouth ulcers, see above—underwent also a serological screening for celiac disease by means of antitissue transglutaminase and antiendomysium antibodies, which gave negative results.

Endoscopy and Histology

All 16 patients underwent colonoscopy with biopsy under conscious sedation, and the examination was extended to the terminal ileum in 6 patients, cecum in 8, transverse colon in 1, and splenic flexure in 1 patient. Using standard biopsy forceps, 1 to 2 biopsies were taken from each colonic segment explored and 5 to 10 biopsies were taken from the terminal ileum. Biopsies were correctly oriented on millipore filters and routinely processed: 5-mm thick sections were cut and stained with hematoxylin and eosin (H&E). Ten of 16 patients (62.5%) had macroscopic abnormalities such as mild focal edema, erythema, and friability of the rectal and/or left colonic mucosa (8 patients, Fig. 1), and lymphoid nodular

Table 1. Major Features of the 16 Patients With Dietary Protein-Induced Proctocolitis

Patient (Sex)	Age (yr)	Symptom Duration	Atopy	PRIST (KU/L)	RAST for Foods	Other GI Symptoms	Systemic Symptoms	Growth	Colonoscopy Features	Eosinophils 10 HPF (40×)	Current Status
1 (M)	11	6 months	No	59.9	Negative	None	None	Normal	Erythema, edema	50–60	Free diet, well
2 (F)	10	6 months	No	8.5	Negative	Anal fissure	None	Normal	Erythema, LNH colon	> 60	Free diet, well
3 (M)	8	3 months	Asthma	22.8	Negative	None	None	Normal	Negative	60	Free diet, well
4 (M)	9	1 month	No	8.8	Negative	None	None	Normal	Negative	> 60	Free diet, well
5 (F)	14	2 yr	AD, asthma	41.9	Negative	None	None	Overweight	Erythema	> 60	Exclusion diet
6 (F)	2	7 months	Mother w/urticaria	11.0	Negative	None	None	Normal	Negative	> 60	Exclusion diet
7 (F)	8	1 yr	No	55.5	+ Milk/egg/wheat	Pain, vomiting	None	Normal	Erythema, edema, LNH	> 60	Exclusion diet
8 (M)	11	15 months	No	36.4	Negative	None	None	Normal	colon/ileum	> 60	Free diet, well
9 (F)	7	4 yr	No	23.9	Negative	Anal fissure	None	Normal	Erythema, LNH ileum	> 60	Free diet, well
10 (F)	13	3 months	Asthma, rhinitis	185.0	Negative	Pain, vomiting, diarrhea	None	Normal	Erythema, LNH colon/ileum	> 60	Exclusion diet
11 (M)	3	3 months	No	2103.0	+ Milk/egg	Pain, hemeatemesis	None	Normal	Erythema, edema	> 60	Exclusion diet
12 (M)	6	3 yr	No	33.0	Negative	Pain, vomiting	None	Normal	Negative	> 60	Exclusion diet
13 (F)	11	6 months	No	40.2	Negative	Nausea, vomiting	None	Normal	Negative	60	Free diet, well
14 (M)	2	1 month	AD	27.2	Negative	Diarrhea	None	Normal	LNH ileum	> 60	Exclusion diet
15 (F)	9	1 month	Mother w/asthma	474	+ Milk/egg	Aphthous stomatitis	None	Normal	LNH colon	> 60	Exclusion diet
16 (F)	8	5 months	No	45.4	Negative	None	None	Overweight	Erythema, edema, LNH colon/ileum	> 60	Exclusion diet

PRIST = radioimmunosorbent test; RAST = radioallergosorbent test; HPF = high power field; AD = atopic dermatitis; LNH = lymphoid nodular hyperplasia.

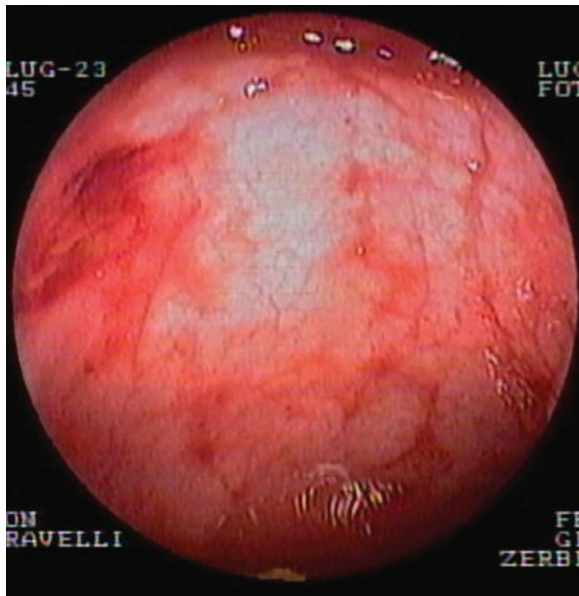


Figure 1. Endoscopic picture showing a slightly distorted vascular pattern with mild edema, erythema, and friability with focal bleeding of the left colonic mucosa in a child with dietary protein-induced proctocolitis.

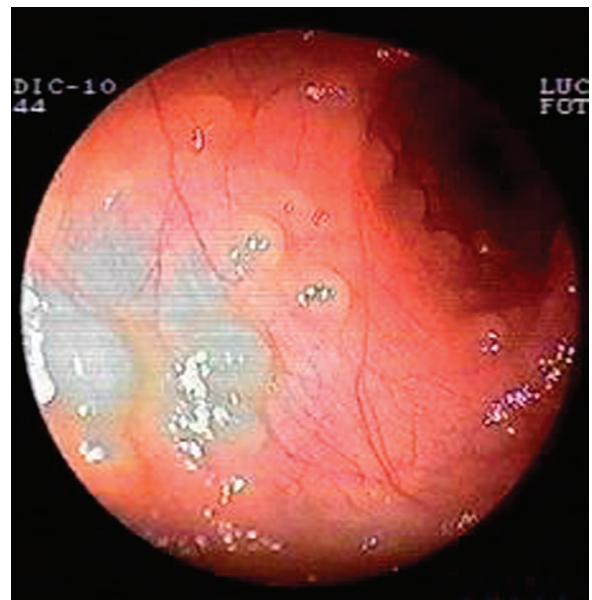


Figure 2. Lymphoid nodular hyperplasia of the left colonic mucosa as seen during colonoscopy in a child with dietary protein-induced proctocolitis.

hyperplasia in the left/transverse colon and/or terminal ileum (7 patients, Figs. 2 and 3). Histological examination showed a uniformly normal crypt architecture with normal goblet cell number and intraepithelial lymphocytes within normal limits, but revealed a significant diffuse eosinophilic infiltration of the lamina propria with >60 eosinophils/10 high power field (HPF, $40\times$) in the biopsies performed in the left colon, sigmoid, and rectum (Figs. 4 and 5). Lymphoid follicle hyperplasia was also reported histologically in all patients, in the same area (Fig. 6). No other significant features such as crypt abscesses, granulomata, or parasites were seen. Upper GI endoscopy with biopsy was carried out in the 5 patients who reported occasional vomiting and/or abdominal pain, and all but one showed normal macroscopic and histologic features in the esophagus, stomach, and duodenum. The one patient with vomiting and hematemesis previously diagnosed as having gastroesophageal reflux disease had a mild eosinophilic infiltration in the duodenum. One patient who reported diarrhea and abdominal pain mainly located in the right lower quadrant, in whom the terminal ileum could not be inspected during colonoscopy, also underwent capsule endoscopy, which showed lymphoid nodular hyperplasia of the terminal ileum. The number of eosinophils in the lamina propria was normal in all patients with other causes of rectal bleeding such as IBD, juvenile polyps, and anal fissures, but was similar to that found in other children with chronic constipation secondary to food allergy (including 8 of the 31 who presented with rectal bleeding related to constipation with anal fissures). In patients with lymphoid nodular hyperplasia, the presence of a major immune deficiency was excluded by the clinical history and by the presence of nor-

mal immunoglobulin levels and T lymphocyte subsets within normal limits.

Response to Exclusion Diet and Food Challenge

All patients were initially prescribed an oligoantigenic diet devoid of cow's milk, egg, and wheat protein. All patients responded satisfactorily to the exclusion diet, and the time to disappearance of overt rectal bleeding ranged from 1 to

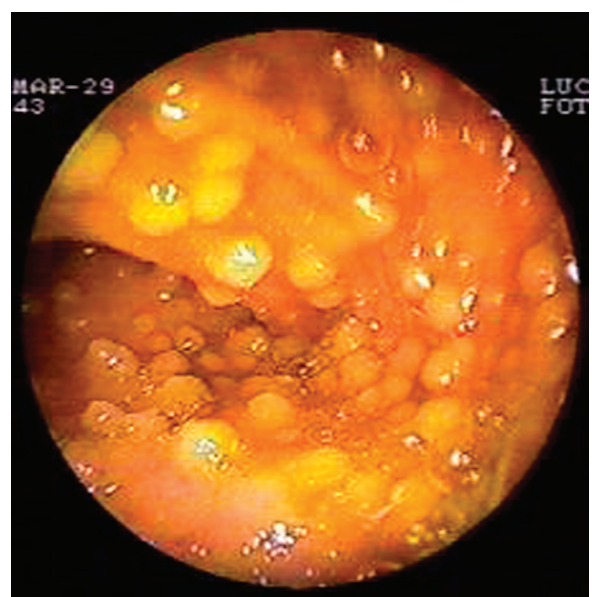


Figure 3. Endoscopic view of a prominent lymphoid nodular hyperplasia of the terminal ileum in another child with dietary protein-induced proctocolitis.

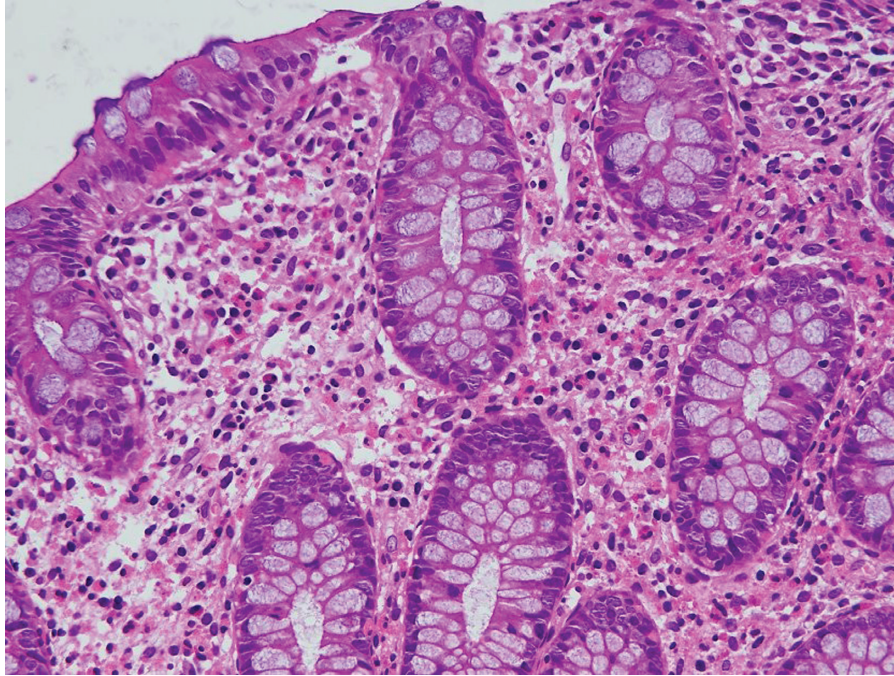


Figure 4. Significant ($>60/10$ HPF) eosinophilic infiltration of the left colonic mucosa in a patient with dietary protein-induced proctocolitis. The crypt architecture appears typically normal (H&E, $40\times$).

7 days. All the other GI symptoms reported by some of the patients also subsided, including the regurgitation and hematemesis in the patient previously diagnosed as having gastroesophageal reflux disease who had not responded to therapy with proton pump inhibitors. Once rectal bleeding had subsided and after 1–3 months of ongoing clinical remission, all patients were instructed to start an open challenge at home by taking wheat, egg, and cow's milk protein *ad libitum* at monthly intervals (*i.e.*, first wheat for one month, then egg for another month, and finally cow's milk). Relapse with rectal bleeding was reported in all patients (with occasional abdominal pain in 2 patients) after a few hours to 11 days and a mean of 3 days from the beginning of the challenge with cow's milk, and two patients also relapsed following challenge with egg and/or wheat.

Follow-Up

Patients were followed up for a mean period of 22 months (range 3 months to 5 yr) after the final diagnosis. Ten patients are still on a cow's milk-free diet (2 also egg- and wheat-free) and they have been taking this diet for a mean period of 27 months (range 3–50 months). In six of them, one or more subsequent attempts to reintroduce cow's milk protein in the diet always resulted in further rectal bleeding, with or without abdominal pain. The other 6 patients—who followed an exclusion diet for a mean period of 9 months (range 7–14 months)—have now been taking a normal diet including cow's milk protein for 4–24 months (mean 10 months) with no further bleeding and no other GI symptoms. During the follow-up period, no patient developed signs or symptoms suggesting inflammatory bowel disease. Four patients—all

of whom had lymphoid nodular hyperplasia in the ileum and/or colon—underwent a second colonoscopy after a 6- to 8-month period of clinical remission on the exclusion diet. Lymphoid nodular hyperplasia was no longer seen in the colon and was considerably reduced in the terminal ileum. The eosinophilic infiltration was significantly reduced in all patients so that no eosinophils or only a few scattered eosinophils could be seen in the left colonic biopsies.

DISCUSSION

Dietary protein-induced proctocolitis—also known as allergic eosinophilic proctocolitis—is one of the most frequent causes of rectal bleeding and is widely regarded as the most common type of colitis in infancy (1–7, 11). Within the patient population referred to our unit for persistent or recurrent rectal bleeding, food protein-induced proctocolitis presenting in childhood represented 18% of cases. In our setting, allergic proctocolitis was a cause of rectal bleeding as common as Crohn's disease, more common than ulcerative colitis, about twice as common as infectious colitis, and was second only to anal fissures related to chronic constipation. Interestingly, the number of children with allergic proctocolitis was only 20% lower (16 vs 20) than that of infants with the same disorder, suggesting that food protein-induced proctocolitis is one of the most common causes of rectal bleeding also in childhood.

Protein-induced proctocolitis of childhood presented mostly as an isolated disorder. However, the presence of vomiting, abdominal pain, and diarrhea in a few patients, the eosinophilic infiltrate in the duodenal mucosa of one such patient and the response of the other GI symptoms to the

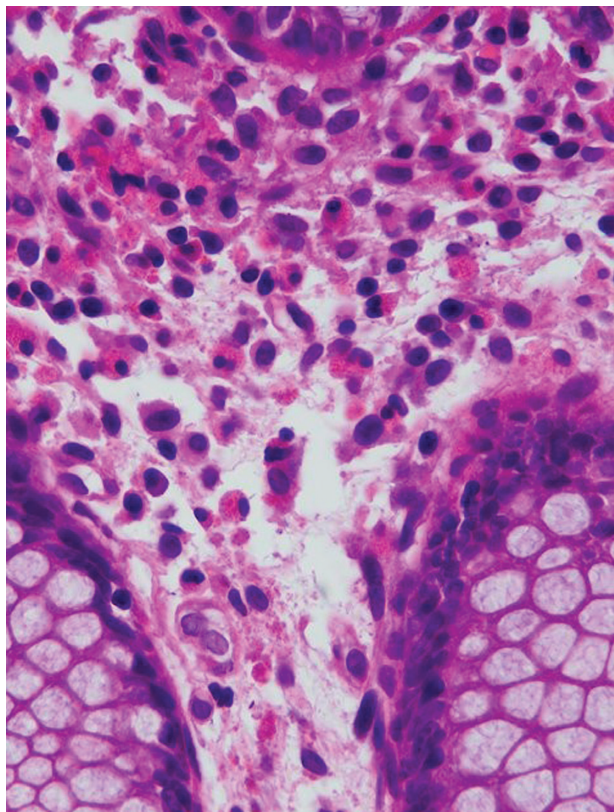


Figure 5. Clusters of eosinophils in the lamina propria of the left colonic mucosa can be more clearly seen at higher magnification (H&E, 100 $\times$).

exclusion diet suggests the possibility that in some cases other segments of the GI tract might also be affected by an allergic inflammation.

The majority of infants with allergic proctocolitis are breast-fed and become sensitized as a result of maternally ingested proteins—most commonly cow's milk protein—excreted in breast milk (1–3, 11). Infants with this disorder look generally healthy and grow normally but have visible streaks of blood or blood mixed with mucus in the stools (1–7). The normal growth and the absence of other significant gastrointestinal and systemic symptoms help to differentiate this disorder from other more serious GI disorders which may result in colitis such as food protein-induced enterocolitis, autoimmune enteropathy, and inflammatory bowel disease (IBD) (4–6, 9, 11, 13). Therefore, the main differential diagnosis is relatively straightforward and essentially includes anal fissures and enteric infections (9, 13). In our patients, cow's milk was the most frequent food—and the only food in most cases—causing the colitis and the rectal bleeding. Like infants, children with food-induced proctocolitis presented with rectal bleeding as the major and often only clinical manifestation. Other GI symptoms such as abdominal pain, vomiting, diarrhea, and constipation were not uncommon but were usually reported as mild and occasional, and apart from one case had not led the patient to medical attention. Signs or symptoms suggesting the possibility of IBD were carefully

sought for but were never reported by our patients. Biochemical markers of IBD such as ESR, CRP, ASCA, and p-ANCA were also normal or negative, as were the stool tests carried out to detect enteric bacterial or parasitic pathogens.

In infants with food-induced proctocolitis, endoscopy is often normal but may sometimes show features of mild proctitis or colitis with edema, erythema, and small erosions, whereas rectal and colonic biopsies typically show an eosinophilic infiltration and occasionally lymphonodular hyperplasia (4–6, 14, 15). The endoscopic and histological findings were remarkably similar in our children with food protein-induced proctocolitis. The only macroscopic alterations were mild focal erythema and edema of the rectal and left colonic mucosa, and lymphoid nodular hyperplasia of the terminal ileum and/or colon, which were noted in more than half of the patients. We did not see spontaneous or active bleeding from the colonic mucosa during endoscopy in any of our patients, so the direct cause of rectal bleeding is not entirely clear. However, lymphoid nodular hyperplasia—both in the small and large intestine—has been consistently associated with food allergy and lower intestinal bleeding in children (16–18), and together with the mucosal erythema was the most likely cause of bleeding in our patients. Likewise, a significant eosinophilic infiltration of the colonic mucosa was detected in all patients and was the most prominent and consistent histological finding. An eosinophilic colitis can be due to parasitic infections (19, 20) but, as mentioned above, stool examination for ova and parasites was negative in all our patients. The eosinophilic infiltration—as well as the lymphoid nodular hyperplasia—was substantially reduced or completely disappeared in the children who were in clinical remission following a few months of cow's milk-free diet, thereby showing that eosinophils are a marker of protein-induced proctocolitis also in childhood and suggesting that eosinophils may play a pathogenetic role in this condition. Although we did not carry out any lymphocyte assay, it is also possible that a T-cell-mediated immune response to food antigens is involved in the pathogenesis of this disorder.

In infants with protein-induced eosinophilic proctocolitis, withdrawal of the offending protein from the baby's or lactating mother's diet is followed by resolution of overt rectal bleeding within 72 h (1, 2, 7) and the clinical response to an appropriate exclusion diet was equally effective in our children with food-induced proctocolitis. Like in the infantile form of dietary protein-induced proctocolitis, tolerance to cow's milk developed in a significant proportion of children after about a year of rigorous exclusion diet.

A possibly similar form of cow's milk protein-related colitis was previously reported in 5 children who presented with rectal bleeding (12). However, in 3 of these 5 children rectal bleeding had started in infancy, one had diarrhea since birth, and only one patient had undergone a food challenge to confirm the diagnosis. Furthermore, only 3 of the 5 patients were reported to have increased eosinophils in the colonic biopsies, though the number of eosinophils was not specified and these eosinophils were found in the right colon

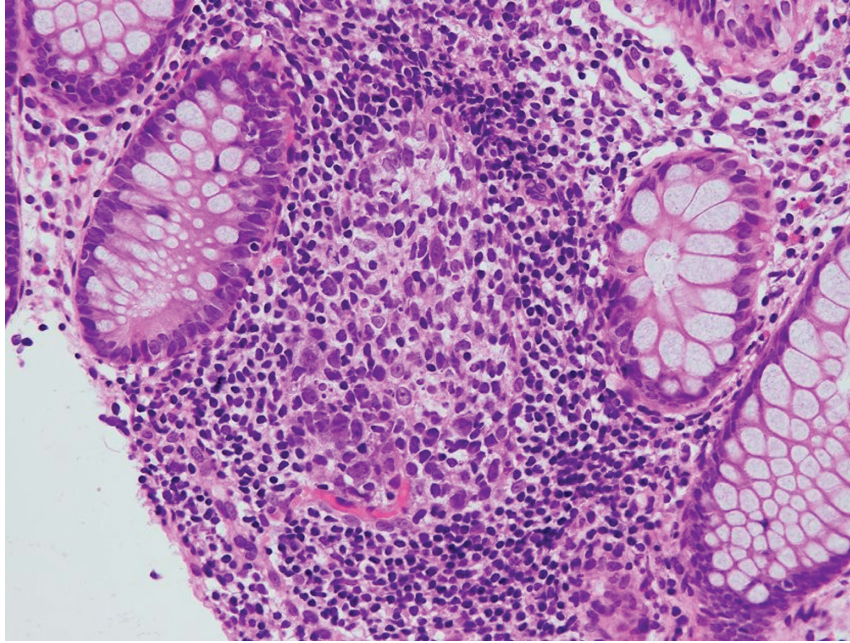


Figure 6. Histological evidence of lymphoid follicle hyperplasia in the left colonic mucosa of a child with dietary protein-induced proctocolitis (H&E, 40 $\times$).

only, a site where—unlike the left colon—eosinophils are normally found. Another form of eosinophilic proctocolitis has previously been reported in a few adolescents and adults (21), but this form is considerably different from the one that we described in children. First, this “late onset” form of eosinophilic colitis typically involved the proximal colon (9, 21). Second, food triggers could not be identified and medical management with drugs such as aminosalicylates and topical or systemic steroids was required (9, 21). Third, severe cases were described which were refractory to or dependent on systemic steroids and required parenteral nutrition and/or immunosuppressive antimetabolite therapy with azathioprine or 6-mercaptopurine (9, 21). This form of eosinophilic colitis is reminiscent of inflammatory bowel disease and indeed several studies have found an association between allergic colitis and later development of inflammatory bowel disease (9). However, this association is controversial and certainly not supported by the clinical, endoscopic, histologic, and therapeutic aspects of the food protein-induced proctocolitis that we have described in children.

On the other hand, food protein-induced proctocolitis seems to partially overlap with other food-related GI disorders of childhood, which present with a variety of symptoms such as constipation, vomiting, and abdominal pain, and are often associated with lymphoid nodular hyperplasia and eosinophilic infiltration of the gut mucosa (18, 22, 23).

In conclusion, we have provided the first formal description of dietary protein-induced proctocolitis in childhood. This disorder shares all the most relevant clinical features with its infantile counterpart, since it is mostly related to cow’s milk hypersensitivity, presents with rectal bleeding as the only or most relevant clinical symptom, does not affect growth, appears to be non-IgE-mediated in most cases, is characterized

by a prominent eosinophilic infiltration of the colonic mucosa, and promptly responds to an exclusion diet. Although the number of our cases and duration of the follow-up period do not allow us to draw definitive conclusions about the natural history of protein-induced proctocolitis of childhood, tolerance to cow’s milk seems to develop within a year in 50% of children with this disorder. Dietary protein-induced proctocolitis appears to be one of the most common causes of colitis in childhood, and as such it should be carefully considered in children presenting with persistent or recurrent rectal bleeding.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Allergic proctocolitis is a common cause of rectal bleeding in infancy.
- Allergic proctocolitis has never been described in children.

What Is New Here

- First formal description of food-related proctocolitis in childhood.
- Allergic proctocolitis is a common cause of rectal bleeding in children.
- Childhood allergic proctocolitis is mostly related to cow’s milk.
- Childhood allergic proctocolitis is characterized by eosinophilic infiltration and lymphonodular hyperplasia.

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CONFLICT OF INTEREST

Guarantor of the article: Alberto Ravelli, M.D.

Specific author contributions: Drs. Ravelli, Chiappa, and Bolognini did the endoscopic evaluation. Drs. Villanacci and Manenti are the pathologists who reviewed all the biopsies. Drs. Chiappa, Bolognini, and Fuoti reviewed all the clinical, laboratory, and follow-up data.

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