

Duodenal bulb nodularity: an endoscopic sign of cow's milk protein allergy in infants?

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To our knowledge, the endoscopic and histologic descriptions of children with cow's milk protein allergy (CMPA) are limited to case descriptions of children with food allergy and lymphoid nodularity of the duodenal bulb.¹ Reports of intestinal lymphonodular hyperplasia (LNH) in children usually refer to colonic or ileal LNH,² and we are unaware of any reports on the significance of duodenal LNH in infants. We report an association between LNH of the duodenal bulb and CMPA in infants with previous diagnoses of gastroesophageal reflux (GER) who subsequently experienced hematemesis and required upper endoscopy.

PATIENTS AND METHODS

Patients

We performed upper endoscopy in infants with a prior diagnosis of GERD who subsequently were brought to our institution with hematemesis during the years 2004 to 2010. By retrospective chart review we collected the following data: age at onset of vomiting/regurgitation, associated GI symptoms, age at onset of hematemesis, age at diagnosis of CMPA, dietary history, atopic disease (eczema, asthma, allergic rhinitis), family history of atopic disease, growth parameters, laboratory findings (hemoglobin concentration, platelet count, blood eosinophil count, serum albumin), endoscopic findings, response to hypoallergenic milk formula and rechallenge with regular cow's milk formula, and follow-up in clinic. The diagnosis of atopic disease was based on general criteria and was accepted only if made by a doctor.

Abbreviations: CMPA, cow's milk protein allergy; GER, gastroesophageal reflux; LNH, lymphonodular hyperplasia.

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Histopathology

During upper endoscopy, multiple biopsies were performed on the duodenal bulb, the second and third parts of the duodenum, the antrum of the stomach, and the lower part of the esophagus. All biopsy specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. Biopsy specimens from the antrum of the stomach were stained with Giemsa stain for the detection of *Helicobacter pylori* organisms. The diagnoses of esophagitis, gastritis, and duodenitis were based on established histopathologic criteria.^{3,4}

Diagnosis of cow's milk protein allergy

All of the infants with suspected CMPA (based on clinical, endoscopic, and histopathologic features) were treated with an elemental milk formula. The diagnosis of CMPA was made if there was complete resolution of GI symptoms after the elimination of cow's milk protein. The recurrence of GI symptoms on oral challenge with a cow's milk formula was used to confirm the diagnosis. Cow's milk-specific IgE antibody determination, celiac testing (IgA tissue transglutaminase [enzyme-linked immunoassay, Inova Diagnostics] and endomyseal antibody determination [immunofluorescence assay, Inova Diagnostics], total IgG level, and total IgA level were obtained in all infants. The local institutional review board approved the study.

RESULTS

The study included 8 infants (5 female), median age 7 months (range, 5-11 months) who were referred because of the development of hematemesis. Their clinical characteristics and abnormal laboratory findings are shown in Table 1. Before referral to our institution, all of the infants were treated by general pediatricians or family practitioners who diagnosed GERD. The infants had been treated by anti-GER measures that included various combinations of positioning, antireflux milk formula or thickening of feedings, domperidone, and acid-suppressive medication (histamine-2 blocker or proton pump inhibitor). The parents did not report improvement of GER as a result of these anti-GER measures.

The hematemesis was described as intermittent and small to moderate in amount. It occurred between 1 and 8 weeks before the infants were brought to our institution (median duration, 4 weeks). Five of the 8 infants had been

TABLE 1. Clinical characteristics of 8 infants with CMPA and duodenal bulb nodularity

Patient	Sex	Age at onset of GI symptoms (mo)	Age at diagnosis of CMPA (mo)	Associated GI symptoms	History of atopic disease	Abnormal laboratory findings*
1	M	birth	6	Colic	+	Platelets 619 Eosinophils 850
2	F	Birth	7	Colic	+	Hb = 10 gm/dl Platelets 639
3	F	6	8	Constipation	+	Hb = 10.5 gm/dl
4	F	5	7	—	+	—
5	M	7	8	Constipation	+	—
6	F	4	11	Diarrhea	—	—
7	F	2	7	Colic FTT	+	Hb 10 gm/dl Platelets 733 Eosinophils 900
8	M	1	5	Colic Diarrhea FTT	+	Hb 9 gm/dl Platelets 750 Albumin 28

GER, Gastroesophageal reflux; CMPA, cow's milk protein allergy; GI, gastrointestinal; F, female; M, male; Hb, hemoglobin, FTT, failure to thrive; +, present; —, not present.

*Normal laboratory values: hemoglobin 12-14 g/dL, eosinophil count $<400 \times 10^6$, platelets $150-450 \times 10^9$, albumin 35-50 g/L.

fed a cow's milk–based formula since birth. Patients 4 and 7 were exclusively breastfed for 2 months and then shifted to a cow's milk–based formula at age 2 months. Patient 3 was exclusively breastfed until 2 months of age, when cow's milk–based formula was added, and the administration of whole cow's milk was started at age 7 months. Seven of 8 infants had individual or family histories of atopic diseases: 4 with eczema, 1 with asthma, 1 with allergic rhinitis, and 3 with family histories of asthma or allergic rhinitis.

In all infants, upper endoscopy demonstrated erythematous, nodular, erosive, and hemorrhagic mucosa of the gastric antrum and body (Fig. 1), multiple nodules limited to the duodenal bulb (Fig. 2A,B), and normal-appearing esophageal mucosa. Histopathologic analysis of biopsy specimens obtained from the duodenal bulb showed LNH with lymphoid nodules composed of dense infiltrations of lymphocytes with germinal centers (Fig. 3A, B). An increased number of intraepithelial lymphocytes and eosinophils in the lamina propria (eosinophil range, 20-25/high-power field) were observed. Biopsy specimens obtained from the duodenal cap in patient 8 showed subtotal villous atrophy, whereas in other patients, biopsy specimens showed normal villi as well as focal flattening of villi at the site of LNH caused by effacement of villi by lymphoid hyperplasia rather than by true villous atrophy. Biopsy specimens obtained from the distal duodenum showed normal villi in all except patient 8, who had

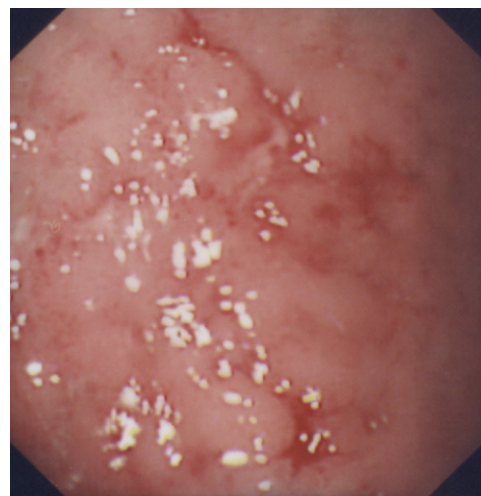


Figure 1. Endoscopic view of nodular, erosive, and hemorrhagic antrum.

subtotal villous atrophy. No LNH could be visualized in biopsy specimens from the distal duodenum. Biopsy specimens obtained from the antral mucosa showed chronic active gastritis with an increased number of lymphocytes and eosinophils in the lamina propria (eosinophil range, 15-20/high-power field), along with eosinophilic cryptitis. Giemsa staining of gastric biopsy specimens from all infants revealed no evidence of *H. pylori* organisms. Specimens from the lower esophagus in patients 2, 6, and 7

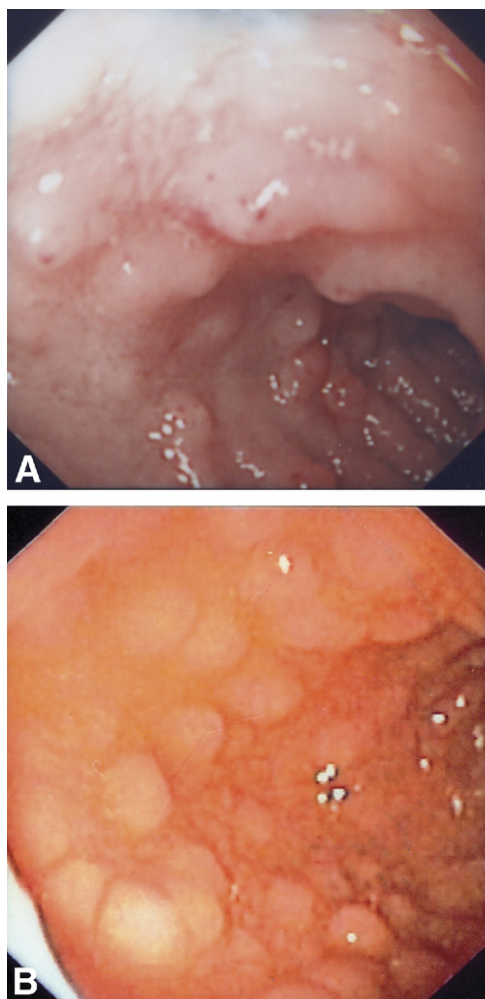


Figure 2. **A**, Endoscopic view of duodenal bulb studied with multiple nodules in patients 1 and **B**, 6, respectively.

showed evidence of reflux esophagitis, evidenced by basal cell hyperplasia, elongation of papillae, and infiltration of the epithelium by a few eosinophils. The results of celiac disease testing were negative in all infants. All the infants had no evidence of cow's milk-specific IgE antibody and normal total IgG and IgA levels.

On the basis of clinical data (GER not responding to anti-GER measures in an infant with individual and/or family history of atopy) and on endoscopic, and histopathologic findings, CMPA was suspected in all 8 infants, and a trial of elemental milk formula was initiated. Complete symptomatic recovery occurred in all infants within 1 week of dietary manipulation. Rechallenge with cow's milk-based formula in 5 infants resulted in the recurrence of GI symptoms within 3 to 5 days. The parents of the remaining 3 infants refused the challenge test; however, the inadvertent switch to a cow's milk-based formula because of the temporary unavailability of elemental milk formula resulted in the recurrence of GI symptoms within 3 to 5 days. GI symptoms resolved after the elemental formula was introduced again. Normalization of abnormal

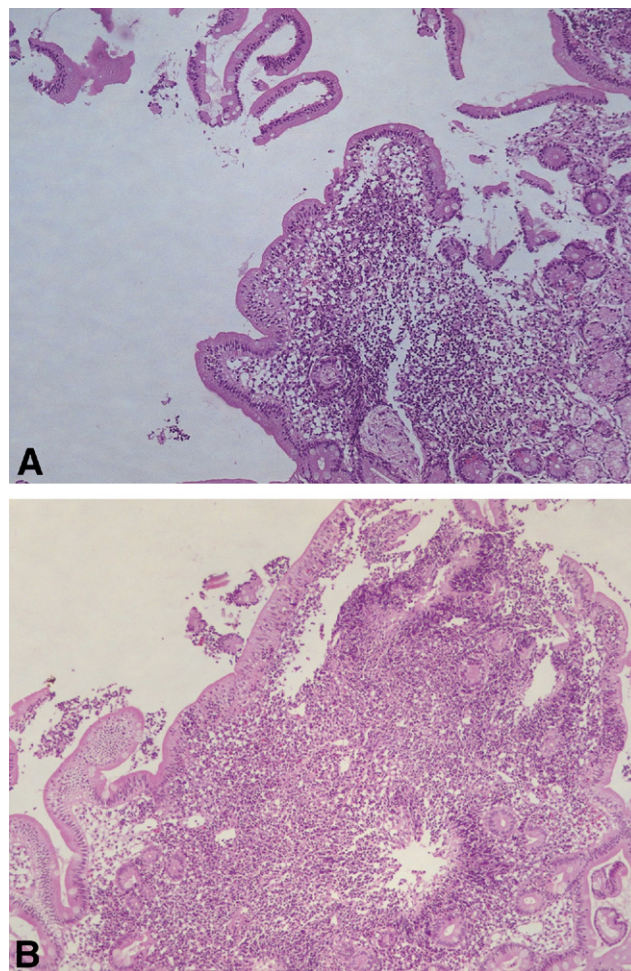


Figure 3. **A**, A lymphoid nodule seen on the duodenal bulb composed of a dense infiltrate of lymphocytes with germinal centers in patients 2 and **B**, 5, respectively. (H&E $\times 100$ high-power field.)

laboratory test results and catch-up in growth were observed within 3 to 6 months during follow-up.

DISCUSSION

The major finding of this study was the recognition that duodenal bulb nodularity caused by LNH is a manifestation of CMPA in infants with hematemesis who previously had diagnoses of GERD. During infancy, CMPA manifests with a wide variety of GI symptoms based on the part of the GI tract involved. Symptoms include diarrhea, constipation, infantile colic, vomiting or regurgitation, failure to thrive, hematemesis, and hematochezia. These symptoms are associated with many GI diseases, and this makes the diagnosis of CMPA difficult for physicians. Infants are scheduled for endoscopic examination only if they experience severe GI symptoms such as failure to thrive, malabsorption, or hematochezia. Thus, meager information exists about the GI endoscopic and histologic lesions observed in infants with CMPA.

The infants in our study received diagnoses of GERD in early infancy. Only because they experienced hematemesis did they undergo endoscopy and received diagnoses of CMPA. Most families reported a history of atopic disease—another clue to the allergic basis of these infants' GI symptoms. The endoscopic and histopathologic findings in LNH suggested the diagnosis of CMPA and led to successful trials with a hypoallergenic elemental milk formula. The positive results of challenge with a cow's milk-based formula confirmed the diagnosis of CMPA. The persistence of GER in infants despite optimal management should alert pediatricians to the possibility of underlying CMPA, and a trial of protein hydrolysate-based or amino acid-based formula or a trial of milk-free diet for the breastfeeding mother should be recommended.⁵

Published reports of intestinal LNH usually refer to its more frequent location in the colon or ileum,² and little information exists about LNH of the duodenal bulb.¹ Nodularity and LNH of the duodenal bulb have been described in the subset of older children with food allergy who presented with recurrent abdominal pain.¹ LNH of the colon related to food allergy has been described in children who presented with hematochezia.² To our knowledge, our study is the first to report on LNH of the duodenal bulb in infants with CMPA, and it highlights the finding of duodenal bulb nodularity as an endoscopic sign of food allergy similar to that observed in older children.¹ However, the observation of duodenal LNH alone cannot be considered as diagnostic of food allergy. It is described in other conditions, including celiac disease,⁶ *H pylori* infection,⁷ common variable immunodeficiency,⁸ IgA deficiency,⁹ and giardiasis.¹⁰ None of our patients had these conditions.

There is a wide spectrum of immunologic reactions to foods. The IgE-mediated GI hypersensitivity reaction typically occurs immediately after ingestion of the offending food and can be diagnosed on the basis of clinical history and the presence of food-specific serum IgE antibody or positive skin prick test results. By contrast, the non-IgE-mediated GI hypersensitivity reaction appears later (usually within 3–5 days) and might mimic the presentation of many nonallergic GI diseases such as GERD. These features and the lack of specific laboratory tests make the diagnosis of non-IgE-mediated food allergy difficult. In this study, the lack of cow's milk protein-specific IgE antibody and the slow onset of GI symptoms after the challenge with cow's milk-based formula suggest that

non-IgE-mediated GI hypersensitivity of late onset is the underlying mechanism for CMPA. We demonstrated an increased infiltrate of intraepithelial lymphocytes in the duodenal mucosa overlying the lymphoid hyperplasia. These intraepithelial lymphocytes were identified by Kokkonen et al¹¹ to be derived from gamma/delta T-cells, an indication of local mucosal immune reactivity to cow's milk protein.

CONCLUSION

Infants with GERD-like symptoms that are unresponsive to treatment who experience hematemesis may have a CMPA that responds to the elimination of cow's milk. Pathologic findings include duodenal bulb nodularity and LNH.

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