



CASE REPORT

Hemorrhagic gastritis due to cow's milk allergy: report of two cases

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Abstract

Objective: to report two cases of infants with hemorrhagic gastritis due to cow's milk allergy.

Description: the clinical features included hematemesis, vomiting and malnutrition. All patients had eosinophilic infiltrate in gastric biopsies and got favorable clinical outcome after cow's milk free diet.

Comments: hemorrhagic gastritis due to cow's milk allergy is an uncommon diagnosis. Clinical findings in 10 patients (including ours) reported with allergic gastritis were vomiting, malnutrition, anemia, and hematemesis. Gastritis occurs in cow's milk allergy in a wide range of severity, and it could remain hidden in most patients. Unless appropriate management is ensued, patients develop severe malnutrition and severe anemia. Allergic compromise of upper gastrointestinal tract might be considered in all vomiting infants particularly if complicated by hematemesis. Diagnosis of allergic gastritis relies on clinical suspicion helped by endoscopy and gastric biopsies.

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The gastrointestinal manifestations of food allergies include chronic diarrhea with malabsorption, rectal bleeding, gastroesophageal reflux, intestinal constipation, and upper digestive hemorrhage.¹⁻⁴ Gastroesophageal reflux (GER) and allergy to cow's milk (CMA) are considered to be the most frequent gastrointestinal disturbances among infants during the first year of life, and are often pathologically related.^{3,5} Persistent vomiting, low weight gain and hematemesis in infants can be the result of GER secondary to CMA gastritis, which are infrequent manifestation of this

pathology.⁶⁻¹⁰ In this study we report on two patients treated at our service over the last six years suffering from hemorrhagic gastritis.

Case Description

Case 1

TASS, male, 24 m, born at full term with no perinatal intercurrent conditions. Complains were vomiting, hematemesis and weight loss. He regurgitated frequently from two months onwards, at five months was interned in another hospital due to two episodes of hematemesis with pallor and irritability. From the second day of internment stools became looser, without blood, but he presented clinical improvement. Digestive endoscopy was performed on the ninth day and was reported as normal, no blood transfusion was necessary and was discharged. The irritability and vomiting continued, as did the weight loss. After forty-five days he presented another hematemesis episode. There was no fever or cutaneous alterations. On this occasion he was brought to our unit. Tests: hemoglobin 10.2 g/dl, hematocrit 32%, 15600 leukocytes (band neutrophils 8%, segmented neutrophils 47%, eosinophils 3%, lymphocytes 36% and monocytes 6%); coagulation test normal; upper digestive endoscopy: hemorrhagic erosive pangastritis which was attributed to the ingestion of acetylsalicylic acid (aspirin) which his mother administered regularly (50 mg/day) to assuage colic. Ranitidine and ferrous sulfate were prescribed and it was recommended that the acetylsalicylic acid and other nonsteroidal antiinflammatory drugs be discontinued. Returned after 15 days reporting numerous episodes of vomiting with blood. On this occasion the patient had Z scores for weight for age and stature for age below -2. An endoscopic examination showed hemorrhagic erosive pangastritis. An antral biopsy showed acute gastritis, ulcers and intense eosinophilic infiltration (24.1 eosinophils / high power field), and was negative for *Helicobacter pylori*; duodenum biopsy showed enteropathy with subtotal villous atrophy and a rectal biopsy showed chronic non-specific colitis without eosinophil infiltration. At 10 months he weighed 8500g and measured 71cm (Z scores for weight for age and stature for age above -1.5). Formula was introduced to his diet at two months. There was no family history of allergy.

He was diagnosed with CMA and put on a diet from which cow's milk protein was excluded and a Soya based formula. He had a total remission of symptoms; there was nutritional recovery and hemoglobin levels normalized. At two years, endoscopy was performed once more and during the procedure cow's milk was infused directly onto the gastric mucosa and the gastric biopsy was collected from this area. There were no macroscopic alterations and histology was normal. Cow's milk was reintroduced and he continued to be asymptomatic, had good evolution and weight gain and after two years' follow up was discharged, asymptomatic, from our care.

Case 2

BSS, female, 24 m, referred suffering from vomiting after feeding and insufficient weight gain. Onset of symptoms was at two months with daily vomiting and traces of blood two to three times a week and three occasions of larger quantities of blood were reported. At three months GER was diagnosed and, cisapride and ranitidine treatment was started. After ten days of treatment, the vomiting with blood persisted and diarrhea began, with a general worsening of condition and she was interned at our unit. Blood culture was positive for *Escherichia coli* and ceftriaxone treatment was started. The patient also presented anemia (hemoglobin 6.2 g/l) and required two blood transfusions. She weighed 5,300 g and measured 57.5 cm at five months (Z scores for weight for age and stature for age were below -2).

The patient was born at full term and had neonatal jaundice, requiring phototherapy, but without other intercurrent conditions. Unskimmed cow's milk was introduced during the first month of life. There was no family history of atopic disease.

Endoscopic examination revealed esophagitis, erosive gastritis on the cardia and anterior corpus wall and duodenitis, and samples of the esophagus, stomach and duodenum were taken. On histological examination, the esophageal mucosa had vascular congestion and some intraepithelial leukocytes, the gastric mucosa presented an area of superficial erosion, edema, vascular congestion, dense and diffuse inflammatory infiltration with lymphocytes, plasmacytes, neutrophils and numerous eosinophils (26.2 /high-power field) present in the glandular epithelium, the crypts and the *muscularis mucosae*. Organisms were also observed which were similar to *Helicobacter pylori*. The duodenal mucosa exhibited increased chorion cellularity, mild eosinophilia and areas of discrete villi flattening. A rectal mucosa biopsy was also taken which presented discretely elevated cellular infiltration of the chorion.

Milk derivatives were excluded from her diet, there was complete resolution of symptoms and she achieved nutritional recovery, using semi-elemental formula. At two years provocation with milk-based formula was performed and the patient remained asymptomatic.

Comments

Upper digestive hemorrhage is an infrequent symptom among infants and can be associated with reflux esophagitis, gastritis due to NSAIDs, gastritis due to stress, primary gastric ulcers and gastritis secondary to CMA. It was originally described by Kravis *et al.*¹⁰ who reported on a three-month old patient suffering from vomiting, hematemesis and low weight gain which disappeared after the exclusion of cow's milk protein from the diet. There are four other reports in the literature involving a further seven patients⁶⁻¹⁰ (Table 1).

Table 1 - Clinical, hystological and endoscopic aspects of eight patients described in literature and two cases of this report with upper digestive hemorrhage due to cow's milk allergy

Authors	n of cases	Age at hematemeses (m)	Age at weaning	Upper digestive endoscopy (n)	Biopsies
Kravis et al. (1967) ¹⁰	1	5 m	1 m	No	No
Coello-Ramirez & Larrossa-Haro ⁶	4	1 patient (< 1 m)	5 to 12 days	Esophagitis (1), gastritis (1), duodenitis (1), antral erosion (3)	No
Brunerie et al. (1986) ⁷	1	5 m	Since birth	Hemorrhagic gastritis and hemorrhagic bulbitis	Antrum: dimorphic mucosa with dedifferentiated epithelium and inflammatory corium, congestive and with hemorrhagic interstitial suffusions. Duodenum: villous atrophy degree II. Rectum: colitis
El Mouzan et al. (1990) ⁸	1	3 m	2 days	Erosive gastritis	Antrum and duodenum: inflammatory infiltrate with tissue eosinophilia
Heldenberg et al.(1993) ⁹	1	5 m	3 months	Erosive gastritis and duodenitis	Antrum and duodenum: inflammatory infiltrate with tissue eosinophilia
Machado et al. (2002) Current description	2	2 m	1-2 months	Erosive or hemorrhagic gastritis Duodenitis (1)	Inflammatory infiltrate with tissue eosinophilia in gastric mucosa (2), villous atrophy (2)

In all of the cases described there was early weaning, during the first three months of life and onset of the clinical status was within the first week of life (one with hematemeses during the first month). While some cases of allergic gastritis have an abrupt onset, many of the patients described had a period of symptoms which were suggestive of reflux, with persistent vomiting, as was observed in the two patients described above. The most common symptom was recurrent vomiting, culminating, in the majority of cases (7/9 patients) in episodes of hematemeses. It is worth pointing out that 22% (2/9) of the patients did not present upper digestive hemorrhage at any point in their evolution. However, infants with refractory GER may be presenting reflux secondary to CMA. The directives of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

include a hypoallergenic diet (trial for one week) in its algorithm for management of infants with GER.^{3,11}

The use of Nonsteroidal Antiinflammatory Drugs (NSAIDs) should always be considered in cases of upper digestive hemorrhage, given that NSAID are widely indicated for the treatment of viral respiratory infections in our locale. These medicines are highly toxic to the gastric mucosa, and experimental studies show that ten minutes after direct exposure to acetylsalicylic acid, mucosa presents superstructural alterations resulting from its toxicity.¹² Histological findings vary, from foveolar hyperplasia, through edema, proliferation of smooth muscle in the muscular layer of the mucosa to normal or slightly elevated numbers of lymphomononuclear cells and absence of polymorphonuclear leukocytes, unless there is erosion of

the area from which the biopsy is taken. In contrast, in allergic gastritis there is an increase in lymphoplasmacyte and neutrophil infiltration with eosinophilia in tissues.¹³ The response to treatment contributes to differential diagnosis, since hemorrhaging ceases soon after the withdrawal of the medication which is causing pharmaceutical gastritis.

Endoscopic abnormalities, especially esophagitis, gastric erosion, duodenal erosion and nodular lymphoid hyperplasia of the duodenum, are common among patients with food allergies, and are probably under diagnosed.¹⁴ Gastric erosion was present in 3/15 patients with abdominal pains and diarrhea, with a diagnosis of food allergy established by placebo-controlled double-blind challenge, although none of them presented digestive hemorrhages.¹⁵ The gastric antrum region always presents an inflammatory process with tissue eosinophilia, whereas in the gastric corpus alterations are focal.¹⁶ Eosinophilia in the gastric mucosa (the gastric region from which biopsies were taken was not specified) was described in 16/28 patients by Kokkonen *et al.*,¹⁴ as against 1/56 of the controls, while eosinophilia in the proximal intestine was similar in both groups of patients. Eosinophilia of the gastric mucosa, important for diagnosis, may also be present with neoplasm, inflammatory fibroid polyp, Crohn's disease, polyarteritis nodosa, parasitic infestations, granulomatous gastritis, hereditary angioneurotic edema, systemic mastocytosis, hypereosinophilic syndrome, histiocytosis X and eosinophilic gastroenteritis; improbable diagnoses during the first week of life.¹⁷

Malabsorption is frequent with CMA, and in a sample of 73 Italian patients, the most frequent symptoms were diarrhea (44/73, 60.3%) and retarded growth (24/73, 32.9%).¹⁸ In allergic gastritis cases that have been described (Table 1), diarrhea (four patients) and insufficient weight gain (seven patients) were common symptoms, which generally indicates small intestine involvement in a number of patients. Even among patients whose gastritis symptoms appeared suddenly, retarded weight gain was observed, suggesting that malabsorption was already present. All of the patients described by Coello-Ramirez and Larrosa-Haro presented abnormal D-xylose absorption tests.⁶ Both of our patients presented villous atrophy, and one of them subtotal villous atrophy in the duodenum biopsy associated with lymphoplasmacyte infiltration. Similar alterations were described by Brunerie *et al.*⁷ Thus, small intestine involvement is common and explains the compromise nutritional status found in reported cases.

First described by Gryboski *et al.* allergic colitis is a common manifestation of CMA, with typical clinical status and primarily occurs among young children.^{2,10,19} Allergic colitis may occur with antigenic stimulation transported by mother's milk, even among patients who have not yet been exposed to heterologous proteins.^{20,21} Diagnosis is aided by histological examination, in which there will be rectal

mucosa infiltration by lymphomononuclear cells and by eosinophils.^{22,23} Our patients did not present allergic colitis, in contrast to the patient described by Brunerie *et al.*⁷ Patients with allergic colitis generally have large intestine involvement, without repercussions for nutritional status, and are appear to be healthy infants. Intestinal constipation may be a manifestation of food allergy, possibly because of pain during evacuation associated with the inflammation of the rectum.⁴

The immunological mechanisms involved in allergic enterocolitis are not well defined.²⁴ Allergies to antigens which are present in food may be the result of altered lymphocyte function.²⁵ Cow's milk is rich in antigenic determinants, of which beta-lactoglobulin is the most significant. This can be recognized by the T cells of allergic patients in a variety of epitopes.²⁶ The stimulation of T cells by the mitogens of patients with food allergies, produces less interferon γ than T lymphocyte stimulation in normal individuals.²⁷ There is also an increase in gamma delta lymphocyte quantities, and also in the $\gamma\delta$ /CD3 relationship.¹⁵ The greater permeability of the intestinal mucosa to macromolecules during the first months of life acts as a precipitate in prematurely weaned patients. The normalization of lymphocyte alterations marks the development of tolerance, generally at the end of the first year of life.²⁸⁻³⁰

The classical diagnosis of food allergy is established by the Goldman criteria, i.e. the resolution of symptoms as a result of an exclusion diet and their return when provoked with the antigen.^{31,32} This may not be appropriate with infants, since the development of tolerance may result in a negative provocation result and early provocation may not be recommendable because of the potential severity of manifestations.³² Other examinations, such as an immunoglobulin E assay by cutaneous or serum test are not sufficiently sensitive for infants and are not recommended.³² The infusion of milk directly onto the gastric mucosa during endoscopy may produce both macroscopic and microscopic lesions in a short time in adult patients, but there are no studies of this with children.³³

It is important to note that the only contribution made by a hemogram to diagnosis is the presence of microcyte anemia. In contrast to allergic colitis, in which up to 40% of the patients present significant eosinophilia, this was not observed with any of the allergic gastritis patients described^{6-10,16}

The exclusion of cow's milk protein produces an important clinical response. The recommended diet should be free of cow's milk and derivatives and formulae for infants made of hydrolyzed protein or soy protein may be employed. The majority of reports in the literature report using a soy protein based formula with success, but as many as 40% of patients may present cross sensitivity.³⁴ Among available reports, only two patients were put on a formula which contained hydrolyzed protein, despite this being the alternative of choice, when available.^{20,21}

Cow's milk allergy compromises gastric mucosa to varying degrees, from histological gastritis to hemorrhagic gastritis - its most severe expression - and can be under diagnosed. Gastritis due to CMA may be the cause of symptoms such as vomiting, irritability and the failure to put on weight even in the absence of any apparent digestive hemorrhage. Diagnosis is eminently clinical and treatment should be initiated rapidly in suspected cases. Upper digestive endoscopy with biopsy should be performed if evolution does not confirm the diagnosis.

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