

INSTRUCTIVE CASE

Cows milk protein enteropathy and granulomatous duodenitis in a newborn

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Abstract: Cow's milk protein enteropathy is a symptom complex that composed of severe diarrhoea and malnutrition. This disorder is caused by non-immunoglobulin E-mediated food allergy. Its clinical features and natural course have been explained in many reports, of different types of cow's milk and soy reactions. In the present article, we describe a newborn patient who presented with chronic diarrhoea and failure to thrive diagnosed as cow's milk protein enteropathy. The duodenal biopsy revealed granulomatous duodenitis which has not been described before. Her clinical and pathological findings responded well to cow's milk elimination. We suggest that food allergies should be considered in differential diagnosis of patients with chronic diarrhoea and failure to thrive.

Key words: cow's milk allergy; granulomatous duodenitis; newborn.

Cows milk allergy is the most common food allergy in early childhood.^{1,2} Approximately one half of the patients present predominantly with intestinal symptoms. Cows milk protein enteropathy (CMPE) is one form of intestinal presentation of cows milk allergy. Its common symptoms are diarrhoea and significant failure to thrive. The age at presentation varies from 1 to 18 months.³ Diagnosis of CMPE is based on the combined findings from clinical history, endoscopy-biopsy, allergen elimination and challenge.

In this report, we present a 2-month-old baby diagnosed with CMPE and responded well to cows milk elimination.

Case Report

A 20-day-old girl was admitted to a local hospital with complaints of yellow coloured mucous diarrhoea, 10–12 times a day, for 1 week's duration. She was first diagnosed with acute gastroenteritis and secondary lactose intolerance and given lactose-free formula. However, her complaints continued, and she was

hospitalised with metabolic acidosis that resolved after proper fluid-electrolyte treatment when she was 1 month old. Because of persistent diarrhoea, however, she was referred to our paediatric gastroenterology unit at the age of 2 months. Her past medical history disclosed an uneventful pregnancy, delivery by elective Caesarean section; birthweight was 3100 g, and there were no perinatal complications. She had not been breastfed and had been given humanised milk formula (Aptamil, Milupa, GmbH, Fulda, Germany) since she was born.

Physical examination on admission disclosed a weight of 3290 g (below 3%) and a height of 54 cm (3%). The infant looked pale, dehydrated and lethargic. No eczema, oral thrush, or napkin excoriation was evident. The liver and spleen were not enlarged, and bowel sounds were normal.

Haematological tests showed the following values: haemoglobin, 8.76 g/dL; haematocrit, 26.1%; white blood cell count, $13 \times 10^9/L$; platelet count, $166 \times 10^9/L$; mean corpuscular volume, 74.2 fL; and red cell distribution width 22. Peripheral smear was normal for age. Biochemical evaluation revealed serum albumin: 2.01 g/dL (normal 3.5–5.5 g/dL), total protein: 4.55 g/dL (normal 6–8 g/dL).

Stool examination revealed a pH of 6, reducing substance and steatocrit were negative. No white or red blood cells were detected on a stool smear. It was negative for occult blood, ova and cysts, cryptosporidium, Clostridium difficile toxin-A and rotavirus, and adenovirus antigens. Sodium and chloride levels were in the normal range.

In the view of the child's significant failure to thrive, chronic diarrhoea and metabolic acidosis discovered at the first hospital admission, investigations were directed toward the possibilities of infection, inborn error of metabolism, immunodeficiency-associated diarrhoea, or CMPE.

Evaluation for metabolic disorders disclosed the renal and liver function tests were normal. Urine and blood amino acid chromatography, tandem mass spectrometry, gas

Key Points

- 1 Cows milk protein allergy should be considered in infants with chronic diarrhoea.
- 2 Delayed diagnosis of gastrointestinal food allergy may result in considerable growth impairment, anaemia, hypoproteinaemia and other deficiency conditions.
- 3 Early recognition and appropriate treatment have important roles in prevention and treatment.

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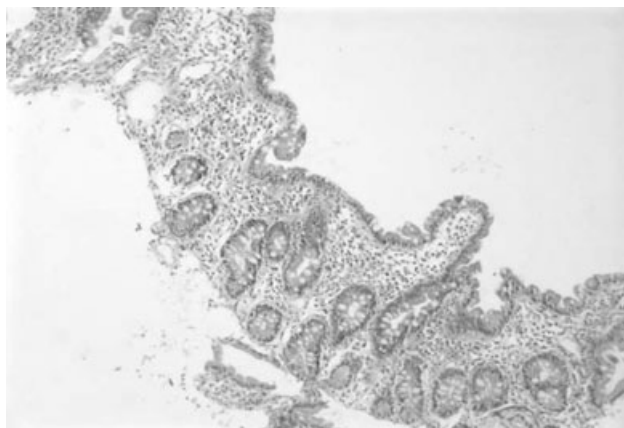


Fig. 1 Total villous atrophy and vacuolisation of enterocytes in the duodenum.

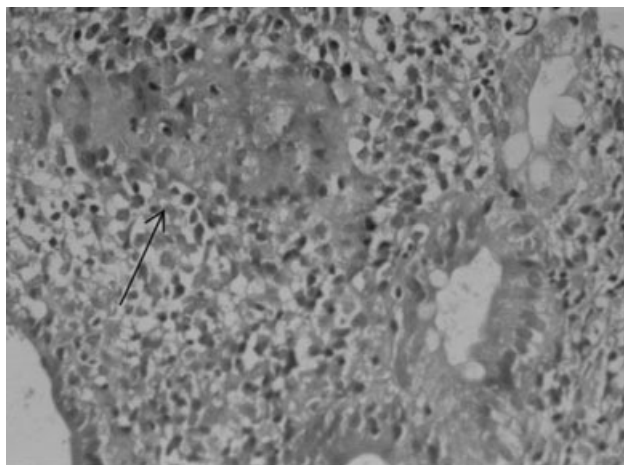


Fig. 2 Non-caseating granulomatous duodenitis.

chromatographic analysis of urinary organic acids and eye examination in search of a metabolic disorder were all unremarkable. Similarly immune deficiency was excluded on the basis of investigations completed. Serum immunoglobulins (Ig) A, G and M were measured at normal ranges for age. Antibody testing for HIV and polymerase chain reaction for CMV were negative. Sweat chloride test was normal (20 mEq/L).

Upper gastrointestinal endoscopy was performed in search of an intestinal mucosal disorder. Thickening and paleness of the duodenal folds were observed. Histological examination of the duodenal biopsy sample showed total villous atrophy, vacuolisation of enterocytes, and multifocal non-caseating granuloma formation (Figs 1,2). Examinations to find the cause of the granulomatous reaction in the duodenum, including acid-fast staining and culture for tuberculosis of the gastric juice, and VDRL for syphilis were all negative. Screening of the parents for tuberculosis was negative. Nitroblue tetrazolium test revealed a normal result. Sigmoidoscopy and colonic biopsy histological findings were normal.

In view of the facts that there was villous atrophy in her duodenal biopsy and exclusion of the other causes of chronic

diarrhoea, we considered CMPE. Her total IgE was 83.3 IU/L (normal 0–15 IU/L), and serum-specific IgE against milk and milk-prick test were negative. We started to feed her exclusively with an amino acid-based formula (Pregomin AS, Milupa). After 10 days of feeding, she started to put on weight, defecation frequency decreased and her watery stool pattern resolved. She was kept on the same feeding formula thereafter. Her weight increased from 3290 g at admission to 4900 g at 5 weeks of exclusive feeding with this formula. No vacuolisation of enterocytes were detected, villous pattern was totally normal, and granulomas were no longer present in the repeated biopsy after 2 months of the treatment. Owing to a lack of permission from her parents, we have not performed a milk challenge. On the last visit, she was 1 year old with normal growth parameters and on a cows milk protein-free diet plus oral calcium supplementation.

Discussion

Food-related gastrointestinal hypersensitivity disorders include food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy (FPIE), and food-induced proctocolitis, as well as eosinophilic gastroenteritis and related disorders. Symptoms of FPIES usually start within 1–2 h after ingestion of food, however, FPIE is a rather slowly evolving disorder within several days or weeks.^{2,3} Cows milk is often the first major food protein ingested by formula-fed infants and may lead to early allergic sensitisation.⁴ There is also evidence that up to 10–15% of children with cows milk allergy have IgE antibodies against soy protein.⁵ Our patient was exclusively fed with cows milk formula that does not contain soy proteins just after birth and severe clinical symptoms were first documented at the second week of life. The diarrhoea became persistent and led to failure to thrive. In the literature, the majority of patients with FPIE do not display evidence of IgE sensitisation.^{2–6} Despite a high serum IgE level in our patient, we could not detect milk-specific IgE, and her skin prick test for cows milk was negative. Finally, we diagnosed her with CMPE, a special form of FPIE.

The diagnosis of CMPE is most often made on the basis of clinical experience and elimination-challenge tests. However, depending on the clinical presentation, upper or lower gastrointestinal biopsies are helpful to adequately identify the disorder at the tissue level and exclude other disorders.^{2,3} On small bowel biopsy, a picture similar to celiac disease, though less pronounced and inconstant, such as patchy blunting of the villi and crypt hyperplasia may be found in CMPE.^{2,6} In one of the first reports concerning duodenal biopsies in CMPE, 31 infants invariably exhibited mucosal damage, with partial villous atrophy being the most usual finding.⁷ These changes were reported as non-specific, and recovery was accomplished with a milk-free diet in 3–13 months. Our patient's pathological examination revealed villous atrophy and non-caseating granulomatous reaction and a milk-free diet resulted in resolution of these findings.

Granulomas are distinctive forms of chronic inflammation characterised by localised activation of activated macrophages around an inciting stimulus. Non-caseating granulomas of the gastrointestinal tract have been reported in Crohn's disease.⁸ However, very early presentation of diarrhoea made Crohn's

disease quite unlikely in our patient. Other causes of intestinal granulomas such as intestinal tuberculosis, sarcoidosis, syphilis and chronic granulomatous disease were excluded on clinical basis. Raafat *et al.*⁹ reported two infants with milk protein-induced proctitis and multinucleated giant cells in colonic biopsies. However, granulomatous duodenitis is not a well-known feature of CMPE. Therefore, we cannot explain the reason for granuloma formation in our patient. Increased intestinal permeability in CMPE has been reported previously.¹⁰ It is possible that a dietary antigen (such as milk) evokes a local inflammatory response that alters the barrier function of the mucosa, resulting in an aberrant increased absorption of luminal antigens. This antigen may stimulate specific T lymphocytes and macrophages, stimulate cytokine secretion, and may lead to granuloma formation in the lamina propria.

We suggest that patients with chronic diarrhoea and failure to thrive should be examined for food allergies. Elimination of a causative agent, as in our patient, may result in considerable improvement both in clinical and pathological findings.

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