

Cow's milk-protein allergy as a cause of anal fistula and fissures: A case report

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Cow's milk-protein intolerance (CMPI) affects a percentage of infants that ranges between 0.3% and 7.5% of the general population,^{1,2} and is therefore one of the most common food intolerances. It is well known that CMPI manifestations more frequently affect the gastrointestinal tract causing vomiting, diarrhea, or both.² However, the spectrum of the possible clinical presentations is very wide,³ and it is a recent discovery that symptoms such as gastroesophageal reflux⁴ and chronic constipation⁵ can often be CMPI manifestations.

Here we report the case of a child with anal fistula and

Abbreviations used

CMPA: Cow's milk-protein allergy

CMPI: Cow's milk-protein intolerance

fissures that were related to CMPI and completely regressed on a cow's milk-free diet.

CASE REPORT

The patient, a boy, was hospitalized in our pediatric division for severe chronic constipation and anal fistula and fissures at the age of 5 years.

Family history was positive for atopic disease (father had rhinitis, and mother had dermatitis), but negative for inflammatory bowel disease.

The patient's birth weight was 3180 gm, and he had been

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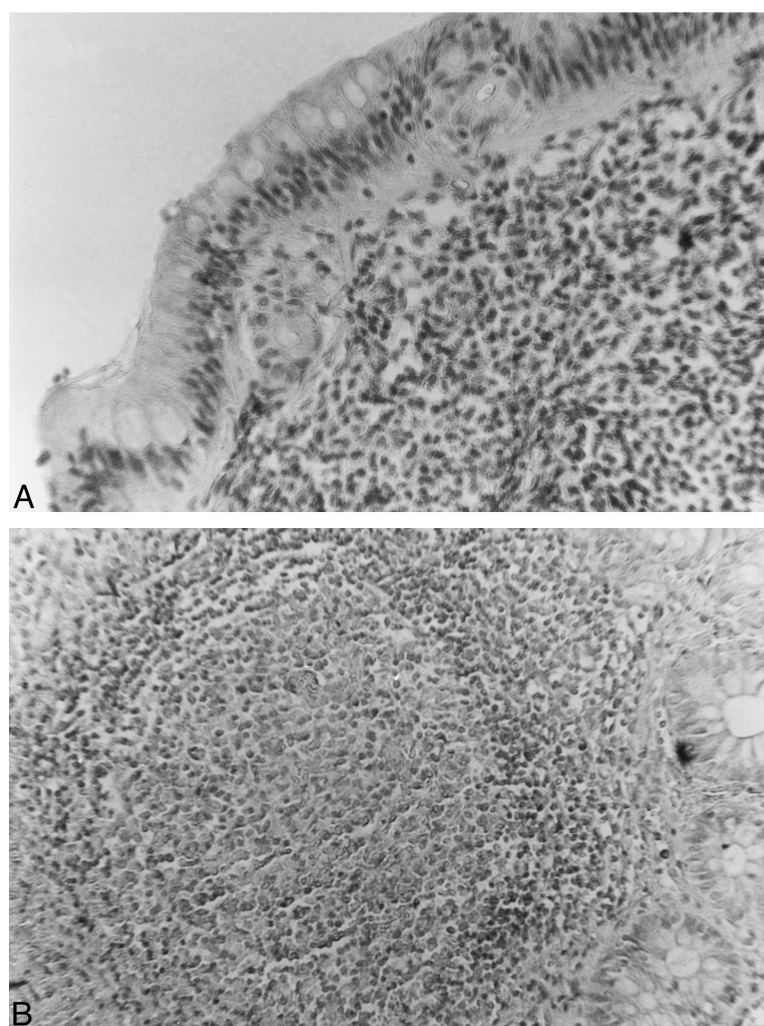


FIG. 1. A, Histologic picture of rectal mucosa showing prismatic metaplasia of epithelium and plasma cell-lymphocyte infiltrate. **B,** Histologic picture of rectal mucosa showing submucosal infiltration with presence of a lymphoid nodule.

bottle-fed since birth with a commercially available formula containing cow's milk protein. He had been hospitalized at the age of 2 months for acute infectious enteritis, and later had several episodes of diarrhea until referred at the age of 6 months. From the age of 6 months, he was hospitalized six times with symptoms of bronchospasm and wheezing. At 12 months, after he was fed honey, a rash appeared but subsequently regressed after administration of corticosteroid and antihistaminic drugs. At the age of 2 years and 6 months, anal fistula and fissures appeared, and 6 months later he had severe constipation (one stool every 3 to 7 days and pain when passing hard stools). Therapeutic attempts to resolve the constipation were not effective (i.e., lactulose, lactitol, bisacodyl, mineral oil, and phosphate enemas). At the age of 4 years he underwent surgery for anal fistula (the fistula was opened) and fissures, but both reappeared 1 month later. Five months before hospitalization in our division, he had urticaria.

On hospitalization, physical examination results were normal except for the perianal lesions. This region was hyperemic and

edematous and showed three fissures and the opening of one anal fistula, which did not extend into the rectum.

Results of all routine hematochemical examinations were within normal limits: erythrocyte sedimentation rate was 5, white blood cell count was $7800/\text{mm}^3$, and the protein C reaction test result was negative. Several parasitologic examinations of the stools were negative. Immunologic tests showed a total IgE level of 12 IU/ml (normal values in our laboratory for subjects in the same age range: <30 IU/ml); number of circulating eosinophils of $100/\text{mm}^3$; serum IgG anti- β -lactoglobulin level of 20% (normal value, $<36\%$); and positive RAST results for casein (15 SU/ml), lactalbumin (12 SU/ml), and β -lactoglobulin (4 SU/ml) (normal values, <1.43 SU/ml).

A plain roentgenogram after administration of a barium enema was negative, and the final tract of the ileum was normal. Rectoscopy, conducted up to 30 cm from the anus, showed signs of proctitis with hyperemia of the mucosa of the final 10 cm of the rectum but without erosions or ulcerations, whereas the remaining intestinal tract examined had a completely normal

aspect. Several biopsy specimens were taken both in the inflamed and in the normal intestinal tracts. The histologic examination of the rectal mucosa specimens taken from the final 10 cm of the anus showed prismatic metaplasia of the epithelium, inflammatory infiltration characterized by the presence of plasma cells and lymphocytes (Fig. 1, *A*), and presence of lymphoid nodules in the tunica propria (Fig. 1, *B*). No histologic alterations were observed in the mucosa specimens from the remaining explored intestine.

On the basis of the clinical history, the laboratory examinations, and the RAST results, we suspected cow's milk-protein allergy (CMPA)-related chronic constipation and proctitis. A cow's milk-free diet was started, excluding cow's milk and all its derivatives. After 1 week of a cow's milk-free diet, bowel frequency normalized (one to two stools/day), with soft feces and no discomfort when passing stools, and the patient was discharged. Contemporaneously we observed a progressive improvement of the anal region with reduced erythema and edema, and after a further 2 weeks, the anal fissures and fistula disappeared. During the following 2 months of a cow's milk-free diet, both bowel movements and the anal region were normal. The child was then rehospitalized to undergo challenge with cow's milk protein. The challenge was performed in a double-blind fashion, as the reaction to the challenge was evaluated by physicians unaware of whether the formula given was a cow's milk derivative or a formula containing hydrolyzed protein. The challenge procedure was the same as previously described.⁴ It was performed with an initial quantity of 10 ml that increased to 250 ml in 3 hours. After the first day, the patient received two 250 ml milk feedings daily. During cow's milk challenge no acute reaction was recorded. However, after 4 days, perianal edema and erythema with one anal fissure reappeared, and the child was already constipated. The cow's milk-free diet was therefore recommenced, and both constipation and anal lesions again completely regressed during the following 15 days.

DISCUSSION

This case report is, to our knowledge, the first to refer to anal fistula and fissures caused by CMPA. These anal lesions were severe, as the patient had formerly had to undergo corrective surgery, but they completely regressed during a cow's milk protein-free diet. In this child the anal fistula was concomitant with chronic constipation, and we have previously reported that this manifestation in young children is often a symptom of CMPA.⁵ Furthermore, we have also observed that patients with CMPA-related constipation had a high frequency of perianal lesions, although less severe than those observed in this case. The patient described here,

in fact, had a fistula that reappeared after surgical treatment, and none of the patients we previously observed had such a severe clinical picture.⁵

The clinical history of the patient, characterized by diarrhea during the first year of life, frequent hospitalization for symptoms of bronchospasm and wheezing, and skin manifestations of allergy, suggested that this child had an atopic disease. Furthermore, the normal inflammation parameter results (i.e., white blood cell count, erythrocyte sedimentation rate, protein C reaction), the normal aspect on plain roentgenography of the colon, the final ansa of the ileum, and the positive RAST result for cow's milk antigens clearly excluded the possible hypothesis of chronic inflammatory bowel disease and pointed to a diagnosis of CMPA, later confirmed by the cow's milk-free diet and subsequent double-blind cow's milk challenge.

Finally, it is important to underline the histologic picture of the rectal mucosa of the patient. Prismatic or cuboid metaplasia of the epithelium, inflammatory infiltration, and lymphoid nodules are characteristics we have observed most frequently in cases of CMPA-related constipation (unpublished data), whereas no histologic indications of Crohn's disease were observed.

In conclusion, this case report suggests the possibility that severe anal and perianal lesions in children may be clinical manifestations of CMPA. This diagnosis must be considered especially in the presence of a clinical history of other "classical" symptoms of CMPA. A large prospective study including a consecutive series of children with anal lesions is, however, necessary to evaluate the frequency of CMPA-related pathogenesis.

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