CASE REPORT

Intestinal goblet cell autoantibody associated enteropathy

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This report describes a case of refractory enteropathy with circulating intestinal goblet cell autoantibodies (IGA). A 19 year old man with hyperthyroidism had suffered from protracted diarrhoea for nearly 10 years. Histological examination showed evidence of collagenous enterocolitis. The diarrhoea did not improve despite fasting under total parenteral nutrition. An immunofluorescence assay demonstrated IGA without anti-enterocyte autoantibodies, the hallmark of autoimmune enteropathy, although other criteria were fulfilled. None of 109 controls, including 55 cases of inflammatory bowel disease and one of lymphocytic colitis, had IGA. This case is considered to be a variant of autoimmune enteropathy, and might be a distinct entity.

Collagenous enterocolitis (CE) is a rare condition characterised by collagenous colitis with involvement of the small intestine.¹ Autoimmune enteropathy (AE) is also a rare disorder defined by the following criteria: protracted diarrhoea, no response to total parenteral nutrition (TPN), predisposition to autoimmune disease, and no immunodeficiency.² We report the first case of CE with circulating autoantibodies to mucin in intestinal goblet cells but not autoantibodies to the cytoplasm of enterocytes, which are the hallmark of AE.

CASE REPORT

A 19 year old Japanese man was admitted to our hospital in July 2001 with a longterm history of continuous watery diarrhoea, which had averaged five to six times daily since December 1991 at the age of 10 years. His past medical history included atopic dermatitis and uveitis at the age of 10 and 17 years, respectively. He suffered from hyperthyroidism two years before admission, and has been treated with thiamazole. His mother has systemic lupus erythematosus and Sjögren's syndrome, and his brother has hypophysial dwarfism and idiopathic leucopenia.

He was 146 cm tall and weighed 32 kg. His bowel movements had increased with distention. Laboratory data on admission showed severe hypokalaemia at a concentration of 1.5 mmol/litre. There were mild liver and pancreatic dysfunction (alanine aminotransferase, 64 U/litre; aspartate aminotransferase, 64 U/litre; serum amylase, 198 U/litre; and trypsin, 675 ng/ml). He had no viral hepatitis B or C infection, but anti-adult T cell leukaemia virus antibody was positive. Quantitative immunoglobulins were normal (IgG, 9340 mg/litre; IgA, 1170 mg/litre; and IgM, 370 mg/litre). All stool cultures were negative. An α 1 antitrypsin test showed no evidence of protein losing enteropathy. A 5-h D-xylose (5 g) absorption test was consistent with severe malabsorption, with a five hour urine collection of 0.3 g (normal, > 1.5 g). Because the diarrhoea continued at an average of 2200 g/day over a six week period, despite fasting under TPN, a diagnosis of coeliac disease could not be made.

Figure 1 (A) Subepithelial collagen bands around tubules are seen in the duodenal mucosa with goblet cell depletion and increased lymphoplasmacytic infiltrate (bar, 50 μ m; haematoxylin and eosin stain). (B) The Masson-trichrome stain showed subepithelial collagen deposits in the sigmoid colon with a striking depletion of goblet cells (bar, 100 μ m).

Abdominal ultrasonography and computed tomography showed no abnormalities. Barium studies of the small intestine and colorectum were normal. Upper and lower endoscopic examinations revealed no gross abnormalities, except for reactive lymphoid hyperplasia in the terminal ileum. However, biopsies of the duodenum and entire colorectum demonstrated subepithelial collagen bands (fig 1). These had variable thickening up to 15 μ m and 25 μ m, respectively, and congo red staining for amyloid was negative. Total villous

Abbreviations: AE, autoimmune enteropathy; CE, collagenous enterocolitis; IE, intestinal goblet cell autoantibody associated enteropathy; IGA, intestinal goblet cell autoantibodies; TPN, total parenteral nutrition

Figure 2 Indirect immunofluorescence assay using a 1/80 dilution of serum reveals positive staining in rat intestinal goblet cells (bar, 100 μ m).

atrophy without intraepithelial lymphocytes was seen in the duodenum and terminal ileum. There was crypt hyperplasia in the duodenum but hypoplasia in the terminal ileum. A diagnosis of CE was made.

Treatment was started with loperamide and colestimide (a bile acid absorption agent), followed by mesalazine (a 5-aminosalicylate) and oral prednisolone (30 mg/day), but there was no therapeutic response. Therefore, we gave intravenous methylprednisolone at a daily dose of 500 mg for three days, and then orally administered prednisolone (30 mg/day). His stools became formed, and a frequency of once a day was achieved. Repeated biopsies showed the disappearance of collagen bands in the duodenum, but they persisted in the colorectum. Prednisolone was reduced to 15 mg/day, and he was discharged. However, one month later he was admitted to another hospital because of the recurrence of diarrhoea, and he required TPN.

Because the above symptoms and findings fulfilled the criteria of AE, we tested for circulating anti-enterocyte autoantibodies using an indirect immunofluorescence technique. Briefly, cryostat sections of the small intestine, colon, and pancreas removed from male Wistar rats were fixed in cold acetone, and incubated with sera at a dilution of 1/40. The sections were washed and incubated with fluorescein isothiocyanate conjugated rabbit antihuman IgG (Dako, Glostrup, Denmark), at a dilution of 1/100, and then observed under a laser scanning microscope (LSM510; Carl Zeiss, Germany).

The immunofluorescence assay using serum from the patient demonstrated antirat intestinal goblet cell autoantibodies (IGA) but not anti-enterocyte autoantibodies (fig 2).

"Intestinal goblet cell autoantibody associated enteropathy may account for some patients with refractory enteropathy, such as unclassified sprue, which is poorly responsive to gluten restriction"

Immunofluorescence was also observed in the mucin of the colonic goblet cells at a titre of 1/80, and in the acinar cells of the pancreas at a titre of 1/40. We also tested for the above autoantibodies in patients with Crohn's disease (n = 32), ulcerative colitis (n = 23), protein losing enteropathy (n = 6), irritable bowel syndrome (n = 6), peptic ulcer (n = 5),

Take home messages

- We describe a case of refractory enteropathy with circulating intestinal goblet cell autoantibodies (IGA), without autoantibodies to the cytoplasm of enterocytes, which is the hallmark of autoimmune enteropathy
- This case is thought to be a variant of autoimmune enteropathy, and might be a distinct entity—IGA associated enteropathy

autoimmune pancreatitis (n = 4), mucosa associated lymphoid tissue lymphoma (n = 3), lymphocytic colitis (n = 1), other disease controls (n = 7), and healthy controls (n = 22). None of the 109 patients had IGA, whereas some had autoantibodies to colonic goblet cells (28 of 109) and pancreatic acinar cells (16 of 109).

DISCUSSION

The only previously documented case of AE demonstrating IGA was that of Moore and colleagues, who described the case of a 9 year old boy.³ Two other similar cases were reported, but there was no information regarding IGA or anticolon goblet cell autoantibodies.^{4,5} The case described by Moore *et al* has several similarities with our case, apart from the presence of IGA: the boys were both older than patients with AE, and there was protracted diarrhoea, abnormal liver function tests, goblet cell depletion, and no appreciable improvement after administering corticosteroids. Our patient exhibited CE, which was absent in Moore's patient. CE has only been reported in 17 patients to our knowledge, and all were women, with an average age of 60 (range, 40–80) years.¹ These findings conflict with the findings in our patient. Therefore, the present case should be diagnosed as a variant of AE rather than CE, namely IGA associated enteropathy (IE). IE may account for some patients with refractory enteropathy, such as unclassified sprue, which is poorly responsive to gluten restriction. Further studies are needed to examine IGA in such forms of enteropathy, including collagenous/lymphocytic colitis, and we believe that IE is a new distinct entity.

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