Familial occurrence of lymphocytic colitis

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HJ Freeman. Familial occurrence of lymphocytic colitis. Can J Gastroenterol 2001;15(11):757-760. The familial occurrence of lymphocytic colitis in a female parent and her two female children is reported. No other genetically based disorder, including celiac disease, was evident. For both children, the age of diagnosis was more than two decades younger than the age of recognition of disease in the parent, and some clinical features, including the requirement for pharmacological agents in both children, suggested that their disease severity was more significant than that of the involved parent. These characteristics of a familial disease have been previously reported and labelled 'genetic anticipation' in some monogenetic forms of neurological disease, as well as in other types of inflammatory bowel diseases, including Crohn's disease. Alternatively, a common cohort effect related to a pathological environmental factor may have played a role in the pathogenesis of this disorder.

Key Words: *Celiac disease; Collagenous colitis; Inflammatory bowel disease; Lymphocytic colitis; Microscopic colitis*

Occurrence familiale de la colite lymphocytaire

RÉSUMÉ : On fait ici état de l'occurrence familiale de la colite lymphocytaire chez une patiente et ses deux filles. Aucune autre maladie d'origine génétique, comme la maladie cæliaque, ne s'est manifestée. Pour les deux enfants, le diagnostic a été posé plus d'une vingtaine d'années avant l'âge qu'avait la mère au moment de son diagnostic et certaines caractéristiques cliniques, dont le traitement pharmacologique chez les deux enfants, donnent à penser que leur maladie est plus grave que chez le parent atteint. Ces caractéristiques de la maladie familiale ont déjà été mentionnées et ont été appelées "anticipation génétique" dans le cas de certaines formes monogénétiques de maladies neurologiques, de même que dans d'autres types de maladies inflammatoires de l'intestin, notamment la maladie de Crohn. Il est également possible qu'un effet de cohorte commune lié à un facteur environnemental pathologique ait joué un rôle dans la pathogenèse de cette maladie.

Collagenous colitis and lymphocytic colitis are two forms of colitis with chronic watery diarrhea and characteristic microscopic features that include chronic inflammation in the lamina propria, damaged colonic epithelium and increased intraepithelial lymphocytes (1-4). Similar changes occur in the colonic mucosa of some, but not all, patients with celiac disease (5-7), and concurrent celiac disease with collagenous or lymphocytic colitis (3,8-11), as well as with refractory sprue (12), have been described. Collagenous colitis was initially described in two independent publications, including an original report from Canada (13,14). Distinct deposits of subepithelial collagen, a prominent pathological feature of collagenous colitis, are not seen in patients with lymphocytic colitis. Most believe that these are separate conditions, although conversion of lymphocytic colitis to collagenous colitis has been described (15). In most series, females are usually affected, often with some other 'autoimmune' disorder, including arthritis or thyroid

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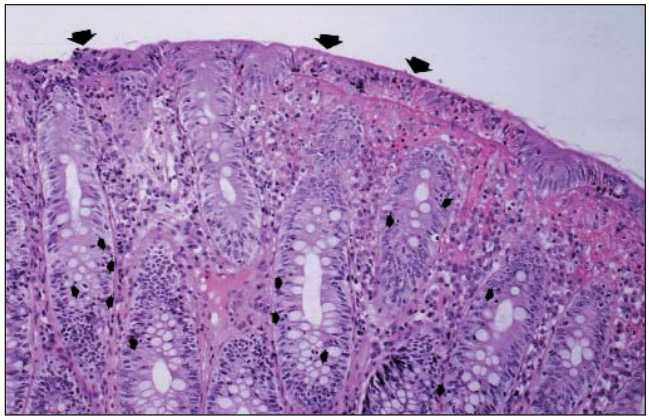

Figure 1) *Colonic biopsy from patient 1 showing lymphocytic colitis. An inflammatory infiltrate is present in the lamina propria with increased numbers of epithelial lymphocytes, particularly in the surface (large arrows) but also in the crypt epithelium (small arrows)*

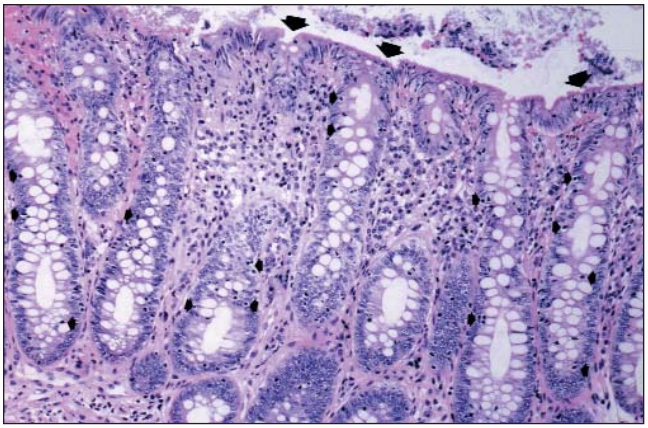

Figure 2) *Colonic biopsy from patient 2 showing lymphocytic colitis. Increased inflammatory cells are present in the lamina propria region with increased numbers of lymphocytes in the surface (large arrows) and crypt epithelium (small arrows). Denuded surface epithelium with epithelial lymphocytosis is also seen*

disease. Treatment, if required, is controversial but often involves anti-inflammatory agents or steroids.

The pathogenesis of these microscopic forms of colitis is not known. A role has been suggested for immunological factors; specific medications, ie, ticlopidine (16); a disorder of the pericryptal myofibroblasts (17); epidemic outbreaks of possibly infectious diarrhea, termed Brainerd diarrhea (18); and a possible pattern in Crohn's disease (19). The critical role of genetic factors has received only limited consideration, possibly because of only recent recognition of this entity. In 1990, van Tilburg et al (20) described the familial occurrence of collagenous colitis in two families, each with two first-degree-related members affected, implying that inherited factors may also be important. In this report, lymphocytic colitis was documented for the first time in three family members – all females with a watery diarrhea syndrome – suggesting that familial factors may also play a role in the pathogenesis of this form of microscopic colitis.

CASE PRESENTATIONS

Patient 1: A 56-year-old woman with watery diarrhea was initially seen in July 1994. She had 'life long' constipation but had suddenly begun having postprandial watery diarrhea for the previous month. In the past, she had occasionally used laxatives but no other medications. She reported that her daughter was diagnosed with 'colitis'. Results of the physical examination were normal. Results of fecal studies for bacterial pathogens and parasites were negative. Laboratory blood test results were normal, including a hemogram, sedimentation rate, and tests for serum iron and proteins, including serum albumin. Results of serological studies for antineutrophil cytoplasmic antibodies (ANCA) were negative. Results of barium studies of the upper gastrointestinal tract, including the small intestine, were normal. Upper gastrointestinal endoscopic evaluation was normal, and biopsies of the duodenum and gastric mucosa were normal. Colonoscopy with mucosal biopsies from different colonic sites was reported to show lymphocytic colitis (Figure 1), based on previously established criteria from the University of British Columbia, Vancouver, British Columbia (5) and elsewhere (21). There was no pigmentation indicative of melanosis coli. A high fibre diet was associated with resolution of her diarrhea, which has not recurred. In 1996, flexible sigmoidoscopy showed visibly normal mucosa, but a biopsy showed persistent, dense epithelial lymphocytosis.

Patient 2: A 29-year-old woman was first evaluated in September 1994. She was the daughter of patient 1 and had recently moved from New York, New York to Vancouver, British Columbia after completion of her university undergraduate program. In New York, 'ulcerative colitis' was diagnosed after she presented with watery, nonbloody diarrhea. A sigmoidoscopy revealed a normal mucosa, but a rectal biopsy showed inflammatory changes. She was treated with sulfasalazine 1 g tid and folic acid 5 mg/day. Results of fecal studies for bacterial or parasitic causes of diarrhea were negative. After two weeks, her symptoms resolved, but she continued using sulfasalazine until June 1994. In Canada, her regimen of sulfasalazine was changed to oral mesalamine 400 mg tid. She remained well for the next three months, but in spite of the medication, watery diarrhea recurred. Results of the physical examination were normal. Results of barium radiographic studies of the upper gastrointestinal tract, including the small intestine, were normal. Blood test results were normal, and results of ANCA serological studies were negative. Colonoscopy results were normal, but colonic biopsies from different sites showed lymphocytic colitis (Figure 2). Results of gastroscopy, and biopsies of the stomach and duodenum were normal. She was treated with increasing doses of oral mesalamine to 800 mg qid. Because of persistent watery diarrhea, treatment with oral prednisone 20 mg was initiated, and her diarrhea resolved after one week. After tapering the prednisone dose over one month, her symptoms did not recur. She returned to graduate studies in New York in September 1996 with no medications but consumed a high fibre diet. From annual

telephone reports, no further recurrence of watery diarrhea had been reported up to December 2000.

Patient 3: A 27-year-old female graduate psychology student was first seen in November 1995 with watery diarrhea. This was associated with abdominal pain, which was relieved by bulking agents, including oral psyllium. She was the second daughter of patient 1. She complained of intermittent episodes of watery, nonbloody diarrhea, sometimes 10 to 15 times daily. She had no other gastrointestinal symptoms or weight loss. She did not use laxatives or other medications. She was investigated in 1987 for watery diarrhea, with fecal cultures and parasite studies, but the results were negative. Results of repeat fecal cultures and parasitology studies in 1995 were negative. Results of blood tests, including a hemogram and sedimentation rate, were normal. An office sigmoidoscopy in 1993 showed granular mucosa, and a rectal biopsy showed inflammatory changes. She was treated with 5-aminosalicylate rectal suppositories for one month, and her diarrhea resolved. In March 1994, while visiting her sister in New York, her diarrhea recurred; flexible sigmoidoscopy suggested 'proctitis with minimal activity', but no biopsies were done. She was treated with oral mesalamine and rectal 5-aminosalicylate suppositories. A coexistent 'irritable bowel syndrome' was diagnosed. Over the next two months, her medications were discontinued. In August 1995, her watery diarrhea recurred. Blood test results were normal, and results of ANCA serological studies were negative. Colonoscopy showed visibly normal mucosa, but biopsies from different sites were reported to show lymphocytic colitis (Figure 3). Results of gastroscopy and biopsies of the stomach and duodenum were normal. She was treated with a high fibre diet, and symptoms had not recurred as of December 2000.

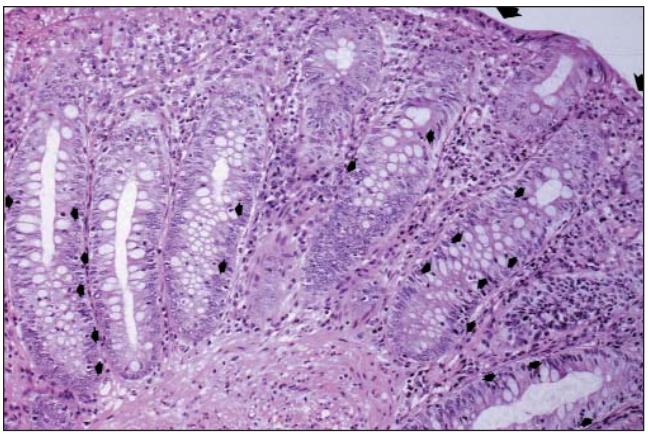

Figure 3) *Colonic biopsy from case 3 showing lymphocytic colitis. A mixed inflammatory infiltrate is present in the lamina propria with increased numbers of intraepithelial lymphocytes present in the surface epithelium (large arrows) and colonic crypts (small arrows)*

DISCUSSION

The diagnosis of lymphocytic colitis is based on a combination of clinical and pathological findings, including chronic, sometimes intermittent, watery diarrhea and the presence of microscopic inflammatory changes in the colonic mucosa with epithelial lymphocytosis (1-5). The cause of lymphocytic colitis is unknown, but it has often been described in celiac disease, a genetically based disorder with an approximate 10% rate of familial involvement (5). Indeed, genetic or inherited factors appear to be critical in the pathogenesis of most forms of inflammatory bowel disease (22). Several studies have described familial forms of ulcerative colitis and Crohn's disease (23-26). In addition, there is a single report of familial collagenous colitis (20), as well as a recent report of a family with collagenous colitis, ulcerative colitis and Crohn's disease (27). The present report of a family with lymphocytic colitis in the absence of histological evidence of celiac disease extends these observations of a familial occurrence to another form of inflammatory bowel disease.

Recent familial studies of inflammatory bowel disease, including Crohn's disease (25,26), have also made a case for genetic anticipation, a phenomenon originally associated with the inheritance of some monogenic neurological disorders (28,29). In parent-child studies, the parent with the initial diagnosis of the specific disorder has had a later age of disease onset than the child. With each successive generation, an apparent increase in disease severity or behaviour has also occurred. In this genetic hypothesis for parent-child involvement with a specific disease, the median age of onset (or diagnosis) in the child has been estimated to be at least two decades younger than that of the parent. In the present report, the age at which lymphocytic colitis was recognized was more than 20 years younger in both daughters than in the mother. The clinical presentations of each of these patients included a watery diarrhea syndrome. For both daughters, however, the treating physicians prescribed anti-inflammatory pharmacological agents, including corticosteroids, to control and resolve symptoms. This was not necessary for the mother, possibly reflecting a limited severity of the disease in the parent compared with that in her children. On the other hand, this could have reflected a difference in physician approach, or, as has been noted elsewhere (26), studies reporting this phenomenon of genetic anticipation in inflammatory bowel disease may not have excluded a cohort effect related to exposure at a specific time for a pathogenic environmental agent. However, in the present family, an 'epidemic' outbreak of chronic watery diarrhea from a common point source (eg, Brainerd diarrhea) was not evident (18).

A familial occurrence of lymphocytic colitis has not been previously described. It is interesting, however, that in the previous description of familial collagenous colitis occurring in two sisters, one had collagenous colitis that later evolved into lymphocytic colitis, suggesting a possible relationship between these two forms of microscopic colitis (17). Further studies are needed to elucidate the extent and nature of the potential familial factors that may play a role in the pathogenesis of these 'atypical' forms of inflammatory bowel disease.

Note: After submission of this manuscript, a recent publication in this journal (30) referred to unpublished data attributed to Jarnerot for a microscopic colitis registry, including five families with two sisters in each family having some form of microscopic colitis. No additional data were provided (30).

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