Prevalence of celiac disease in collagenous and lymphocytic colitis

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HR Gillett, HJ Freeman. Prevalence of celiac disease in collagenous and lymphocytic colitis. *Can J Gastroenterol* 2000;14(11):919-921. Both collagenous and lymphocytic colitis have been described in patients with celiac disease, suggesting an association between the conditions. Over the past few years, the availability, sensitivity and specificity of serological markers for celiac disease have improved – the most recent advancement being the description of tissue transglutaminase as the major antigen for endomysium antibody. A quantitative ELISA was used to measure titres of immunoglobulin A (IgA) antibody to tissue transglutaminase (tTG) along with an immunofluorescent technique for IgA endomysium antibody (EmA) in 15 patients with lymphocytic colitis and eight with collagenous colitis to determine whether celiac disease latency could be detected. One patient with lymphocytic colitis demonstrated both elevated titres of tTG antibody and positive EmA, and small bowel biopsy confirmed celiac disease. One patient with collagenous colitis had a slightly elevated titre of tTG antibody with a negative EmA, and results of a small bowel biopsy were normal. Three other patients with lymphocytic colitis were already treated for previously diagnosed celiac disease. The prevalence of celiac disease occurring in lymphocytic colitis was found to be 27%, but no cases of celiac disease in association with collagenous colitis were found.

Key Words: Celiac disease; Collagenous colitis; Endomysium antibody; Lymphocytic colitis; Tissue transglutaminase

Prévalence de la maladie coeliaque dans les colites collagène et lymphocytaire

RÉSUMÉ: La colite lymphocytaire et la colite collagène ont toutes deux été signalées chez des patients souffrant de la maladie coeliaque, ce qui donne à penser qu'il existe un lien entre les deux maladies. L'analyse des marqueurs sérologiques de la maladie coeliaque ainsi que leur sensibilité et leur spécificité se sont améliorées au cours des dernières années, le progrès le plus notable étant la description de la transglutaminase tissulaire comme le principal antigène de l'anticorps anti-endomysium. On a procédé à un titrage des anticorps anti-transglutaminase tissulaire (TGt) de type immunoglobuline A (IgA) par la méthode ELISA ainsi qu'à une épreuve d'immunofluorescence pour la détection des anticorps (Ac) anti-endomysium chez quinze patients souffrant de colite lymphocytaire et huit patients souffrant de colite collagène pour savoir s'il était possible de déceler une maladie coeliaque latente. Un patient atteint de colite lymphocytaire présentait à la fois un titre élevé d'anticorps anti-TGt et une épreuve positive d'Ac anti-endomysium; une petite biopsie de l'intestin a confirmé la présence de la maladie coeliaque. Par contre, un autre patient atteint de colite collagène présentait un titre légèrement élevé d'anticorps anti-TGt et une épreuve négative d'Ac anti-endomysium; la biopsie de l'intestin s'est avérée normale. Trois autres patients souffrant de colite lymphocytaire avaient déjà été traités pour une maladie coeliaque diagnostiquée antérieurement. La prévalence de la maladie coeliaque s'est élevée à 27 % chez les patients atteints de colite lymphocytaire, mais aucun cas de maladie coeliaque n'a été associé à la colite collagène.

Collagenous colitis (CC) and lymphocytic colitis (LC) have similar clinical and histopathological features; chronic watery diarrhea occurs with prominent chronic inflammation in the lamina propria, damaged colorectal epithelium and increased intraepithelial lymphocytes (1,2). Similar features are seen within the small intestine in patients with celiac disease, and there have been reports of

concurrent celiac disease and collagenous or lymphocytic colitis (3-6).

Immunoglobulin A (IgA) endomysium antibody (EmA) is a sensitive and specific serological marker for celiac disease (7-9). Tissue transglutaminase (tTG) has been identified as the major antigen for EmA (10), enabling the establishment of an ELISA to measure IgA tTG antibody. This ELISA has

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Received for publication March 19, 1999. Accepted November 30, 1999

TABLE 1
Small bowel biopsy reports of 22 patients with collagenous or lymphocytic colitis

Number of biopsies	Histological report
20	Normal
1	Moderately severe villous atrophy and crypt hyperplasia
1	Normal villous architecture but increased numbers of intraepithelial lymphocytes

Figure 1) Titres of immunoglobulin A (IgA) tissue transglutaminase (tTG) antibody in patients with collagenous colitis (CC) and lymphocytic colitis (LC). The reference range is 4 to 60 arbitrary units (AU)/mL. The horizontal line indicates the upper limit of the reference range

been found to be both sensitive and specific for celiac disease (11,12). We investigated whether patients with CC or LC exhibited IgA EmA or IgA tTG antibody in serum.

PATIENTS AND METHODS

Patients: Twenty-three patients – 20 female and three male – were studied. Fifteen had a diagnosis of lymphocytic colitis and eight collagenous colitis. The mean age was 56.7 years (range 25.7 to 83.3 years). Fifteen patients (11 with LC and four with CC) were not on medication for their colitis at the time of the study; three (two CC, one LC) were on oral corticosteroids, three (two CC, one LC) were on acetylsalicylic acid preparations, and two with LC were on antidiarrheal agents.

Three patients with LC had also received a diagnosis of celiac disease and were treated with a gluten-free diet.

Serum was collected from each patient and tested for IgA EmA and IgA tTG antibodies.

Serological testing: IgA EmA was tested by using indirect immunofluorescence against human umbilical cord as described by Ladinser et al (8). Samples were tested at 1:5 dilution.

IgA antibodies to tTG were detected using an ELISA, as described by Dieterich et al (11). Samples were tested initially at 1:5 dilution, with high samples diluted further until

a titre was obtained. Titres were measured in arbitrary units (AU)/mL by comparison with a standard serum.

Small bowel biopsy: Distal duodenal biopsies were taken endoscopically and examined by the hospital pathology department and by one of the authors.

RESULTS

Small bowel biopsy: Biopsy results of 22 of 23 patients are shown in Table 1. The one patient with increased intraepithelial lymphocytes as the only abnormality was a woman in whom celiac disease had been diagnosed 24 years earlier and had been on a strict gluten-free diet during that time.

Serological results: Titres of IgA tTG antibody ranged from 6 to 73,000 AU/mL, with a median of 13.5 AU/mL (reference range 4 to 60 AU/mL). The titres are shown in Figure 1. Three patients had raised titres. The first, a 63-year-old woman with CC, had a titre of 68 AU/mL. Results of a small bowel biopsy were normal, and the authors plan to monitor clinical symptoms and repeat the serological titres.

The second patient was a man in whom celiac disease and LC had been simultaneously diagnosed nine months earlier. His tTG antibody titre was 209 AU/mL. His symptoms had completely resolved with gluten-free diet; therefore, a further duodenal biopsy was not performed.

The third patient had a tTG antibody titre of 73,000 AU/mL. He was a 78-year-old man with LC in whom small bowel biopsy showed moderately severe villous atrophy with crypt hyperplasia. This man was the only patient who demonstrated IgA EmA; the remaining samples were all negative.

DISCUSSION

CC was first described in three patients with a watery diarrhea syndrome in two independent reports in 1976 (13,14). Both described a subepithelial collagen band in the lamina propria associated with increased lamina propria lymphocytes and plasma cells in macroscopically normal colonic mucosa. Several other reports of similar clinical and pathological features have been published since then. Women are more commonly affected (nine to one), and typically the patient presents in the sixth to seventh decade of life (1).

LC demonstrates similar clinical features to CC, particularly watery diarrhea. Typically, the colonic mucosa also appears normal macroscopically, but histologically shows surface epithelial damage with increased intraepithelial lymphocytes and chronic inflammation in the lamina propria, but no subepithelial band occurs. Unlike CC, LC affects males and females equally (1). CC and LC should be considered to be separate but similar conditions, although conversion of LC to CC has been described in a few cases (1,2).

In celiac disease, villous atrophy occurs along with crypt hyperplasia and increased crypt mitoses. Lymphocytes are increased in both the epithelium and the lamina propria (15). In addition, colonic lymphocytosis is frequently seen in patients with celiac disease (16). In contrast, however, celiac disease is closely linked with human leukocyte antigen (HLA) DR3, DQ2, but no HLA associations have been

found for either CC or LC (2). Celiac disease occurring in cases of both CC and LC has been described in the literature (3-6). Two of these studies looked for celiac disease in patients diagnosed with CC (3,6). The first study found four cases of celiac disease in 10 patients with CC, the second found a much lower prevalence, with only one case out of 45. Two further studies (17,18) tested patients with CC or LC for serological markers of celiac disease. IgA antireticulin antibodies were found in one of 29 patients with CC and none of 21 with LC – a similar prevalence to that found in the general population (17). IgA EmA was present in one patient of 38 with CC (18).

In our own department, loading the diet of two patients with LC with gluten failed to induce small intestinal changes (19), suggesting that, in these patients at least, no celiac latency existed. In view of this, 15 patients with LC and eight with CC were tested for IgA EmA and IgA tTG antibody to look for serological evidence of celiac disease. One new case of celiac disease, in addition to three previously diagnosed cases, was found – all patients with coexisting LC – resulting in a prevalence of four of 15 (27%). None of the eight patients with CC had biopsy-proven celiac disease, although one woman did have slightly elevated titres of IgA tTG antibody. Although other serological markers have been found to predict development of celiac disease (20,21), this has not been proved with tTG antibody. If we had chosen to use

these serological tests as screening tools to identify patients in whom small bowel biopsy was indicated, no patient with celiac disease would have been missed and only one patient would have undergone a biopsy for a false positive tTG antibody titre. This suggests, therefore, that celiac serology may be a useful screening tool to identify patients with CC or LC in whom small bowel biopsy is indicated.

A direct pathogenic link between celiac disease and either CC or LC has not yet been elucidated. Although all three conditions demonstrate similar histopathological features, it is unclear whether the reported coexisting cases have occurred by chance or are due to a common mechanism. The studies that have been performed to try to clarify whether an association exists, including this one, have all involved small numbers of cases, making conclusions impossible. The reported incidences of CC and LC vary from 0.3% to 5% of patients investigated for chronic diarrhea (22,23), and the relative rarity of these conditions probably accounts for the difficulty in studying large numbers of cases. Ideally, a large multicentre study to examine the prevalence of celiac disease occurring in association with these colitides should be performed.

ACKNOWLEDGEMENTS: This work has been supported by a research grant from the Canadian Celiac Association, Vancouver Chapter, Vancouver, British Columbia.

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