

An Association Between Microscopic Colitis and Celiac Disease

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BACKGROUND & AIMS: Microscopic colitis has been associated with celiac disease. We aimed to determine the extent and significance of this relationship. **METHODS:** A prospectively maintained database of celiac disease patients, seen between 1981 and 2006, was analyzed. Standardized morbidity ratios (SMR) were calculated using a general population study of microscopic colitis as the reference group. Statistical analysis was conducted using the Student *t* test, Pearson χ^2 test, or Fisher exact test. **RESULTS:** Microscopic colitis was found in 44 of 1009 patients (4.3%); this represented a 70-fold increased risk for individuals with celiac disease to have microscopic colitis, compared with the general population (SMR, 72.39; 95% confidence interval [CI], 52.52–95.36). The celiac disease patients with microscopic colitis were older ($P = .0001$) and had more severe villous atrophy ($P = .002$) than the celiac disease patients without microscopic colitis. Microscopic colitis was diagnosed after celiac disease in 64% of the patients, simultaneously in 25%, and before celiac disease in 11% ($P = .0001$). Pancolitis predominated, though 16% had colitis limited to the right colon. Steroid or immunosuppressant therapies were required in 66% of the celiac disease patients with microscopic colitis and given as maintenance therapy to 50% of these patients. Follow-up biopsies revealed that the colitis persisted in 57% of the patients with celiac disease and microscopic colitis, despite improved diarrhea symptoms; the diarrhea resolved in most of the patients. **CONCLUSIONS: Microscopic colitis is more common in patients with celiac disease than in the general population. Patients with celiac disease and microscopic colitis have more severe villous atrophy and frequently require steroids or immunosuppressant therapies to control diarrhea.**

Celiac disease is an autoimmune disorder characterized by intolerance of gluten, the storage protein of wheat and similar grains.¹ Gluten exposure leads to damage of the small bowel mucosa characterized by intraepithelial lymphocytosis, crypt hypertrophy, and varying degrees of villous atrophy. Withdrawal of gluten reverses the pathological changes.² Persistent symptoms despite the diet are, however, common, estimated to occur in 7% to 30% of individuals with celiac disease.³ Several studies have demonstrated that microscopic colitis is among the causes of persistent or recurrent diarrhea in patients with celiac disease, despite adherence to the diet.^{4–6}

Microscopic colitis is a disorder characterized by nonbloody, watery diarrhea.^{7,8} Microscopic colitis is diagnosed by the finding of abnormal colonic histology in the absence of macroscopic (endoscopic) abnormalities of the colonic mucosa. It is subdivided into 2 entities on the basis of histological findings: collagenous colitis and lymphocytic colitis.⁹ The etiology of

microscopic colitis is unknown; however, the course is usually mild and long term prognosis good.¹⁰

The association of celiac disease and microscopic colitis is well established.^{6,11–14} There is, however, controversy as to whether all intraepithelial lymphocytosis found in colonic biopsies from individuals with celiac disease represents lymphocytic colitis or a manifestation of gluten sensitivity.¹⁵ In addition, there are few data on the extent of the association of celiac disease and microscopic colitis, compared with the general population data, nor about the natural history of microscopic colitis in patients with celiac disease. We therefore addressed these questions by analyzing the clinical and pathological findings in a large cohort of patients with celiac disease.

Methods

Subjects

Patients were selected from an anonymized database of 1009 patients with celiac disease who attended the Celiac Disease Center at Columbia University in New York, a tertiary referral center. The majority of patients seen come from the metropolitan area of New York City. In addition the majority are self-referred (70%). All patients are prospectively entered into the database after giving informed consent about the database. To be included in this study, adult patients were required to have biopsy-proven celiac disease and microscopic colitis. The demographic composition of the entire cohort was as follows: 64.6% women, 99% Caucasian, and mean age at diagnosis of celiac disease of 41.3 (SD \pm 16.7) years. Our database demographics are similar to a community-drawn sample of 1602 adult celiac disease patients reported previously.¹⁶ This study was approved by the Institutional Review Board. We are not aware of whether any of the patients lost to follow-up had microscopic colitis diagnosed elsewhere. All patients were seen by 1 physician.

Microscopic colitis was diagnosed when >20 intraepithelial lymphocytes per 100 epithelial cells were identified with none or minimal distortion of crypt architecture, and mild chronic lymphoplasmacytic inflammation of the lamina propria was identified in colonic biopsies taken from endoscopically normal appearing areas. Collagenous colitis was identified by the presence of a thickened band of subepithelial collagen (>10 mm in width). Data were collected regarding age, sex, dates of diagnosis, treatments, and clinical course. Pathology of the original

Abbreviations used in this paper: CI, confidence interval; PVA, partial villous atrophy; SMR, standardized morbidity ratio; S/TVA, subtotal/total villous atrophy.

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1542-3565/09/\$36.00
doi:10.1016/j.cgh.2009.07.011

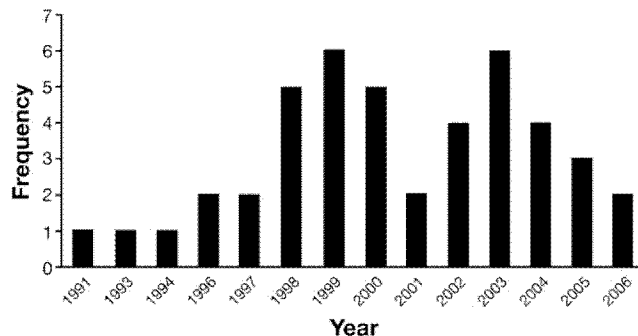


Figure 1. Annual frequency of microscopic colitis in a cohort with celiac disease.

and follow-up biopsies was reviewed. Duodenal biopsies were graded using the modified Marsh classification: partial villous atrophy (PVA) refers to Marsh IIIA stage, and subtotal/total villous atrophy (S/TVA) refers to Marsh IIIB and IIIC.¹⁷ Marsh I and II lesions representing normal villous appearance with intraepithelial lymphocytosis (Marsh I) and crypt hypertrophy (Marsh II) were also identified. Polymerase chain reaction analysis for T cell receptor (TCR) gene rearrangement was performed on formalin-fixed paraffin-embedded small bowel biopsies followed by polyacrylamide gel electrophoresis and heteroduplex analysis.¹⁸

Data Analysis

To determine the relative association between celiac disease and microscopic colitis and its subtypes, lymphocytic colitis and collagenous colitis, standardized morbidity ratios (SMR; age and sex matched) were calculated. We used the general population incidence as reported by Pardi et al in their survey of the incidence and prevalence of microscopic colitis in a North American population (Olmstead County, Minnesota).¹⁹ As our population is overwhelmingly (>98%) Caucasian, comparison with the above population (89% non-Hispanic white) appeared appropriate. The time course of the study by Pardi et al (1985–2001) was similar to the period of patient accrual in our database (1981–2006); however in the analysis we restricted comparison of Pardi's cohort to those patients seen by us up until 2001.

Statistical analysis was conducted using the Student *t* test, Pearson χ^2 test, or Fisher exact test, where appropriate. In terms

of grading patients' response to treatment, patients were categorized as "good responders" and "poor responders." "Good" versus "poor" response to a specific medication was determined by the investigators using a global assessment of persistent diarrhea after at least 3 months of the prescribed treatment. Patients with no change or worsening of their symptoms were defined as poor responders; patients experiencing some degree of remission were defined as good responders, even if symptoms did not remit entirely.

Kaplan–Meier survival analysis was used to describe and compare the natural history of microscopic colitis in celiac disease patients by subtype (lymphocytic versus collagenous), and by gender. For all analyses, significance was determined at the $P < .05$ level (two-tailed).

Results

Four percent ($n = 44$) of the patients in our cohort had microscopic colitis, 33 lymphocytic colitis, and 11 collagenous colitis. All cases were diagnosed after 1990. Subsequent to this time point these 44 cases represented 5.1% of the cohort. The annual incidence is shown in Figure 1. As shown in Table 1, the mean age of diagnosis of celiac disease in those with microscopic colitis was significantly greater than those without microscopic colitis ($P < .0001$). There was no difference in the gender distribution of the microscopic colitis group compared with the celiac disease cohort ($P = .11$). However, among the 2 subtypes of microscopic colitis, collagenous colitis only occurred in females, ($P < .05$).

Although both groups of patients with lymphocytic colitis and collagenous colitis did not differ in the mean age at presentation, a bimodal age distribution was noted in women with lymphocytic colitis and celiac disease, with peaks at 30–39 years and 70–79 years. The age distribution of collagenous colitis, however, was unimodal, with a peak at 60–69 years. As for other risk factors for microscopic colitis, none of the patients were smokers and 68% had at least 1 other autoimmune disorder. We are not aware of nonsteroidal anti-inflammatory drug use in this cohort.

Occurrence of Microscopic Colitis in Celiac Disease Compared With the General Population

We calculated the standardized morbidity ratios (SMR) for microscopic colitis and its subtypes in celiac disease patients

Table 1. Demographic Characteristics of Study Population

	Celiac disease		P value
	Celiac disease cohort ($n = 965$)	Microscopic colitis ($n = 44$)	
Age at diagnosis of CD (Mean \pm SD)	42.7 \pm 17.9	53.2 \pm 14.6	.0001
Sex ratio (F:M)	2.1:1	3.9:1	.11
	Microscopic colitis		P value
	Lymphocytic colitis ($n = 33$)	Collagenous colitis ($n = 11$)	
Age at diagnosis of MC (Mean \pm SD)	57.2 \pm 15.8	56.6 \pm 9.7	NS
Sex ratio (F:M)	2.7:1	All female	.05

CD, celiac disease; F, female; M, male; MC, microscopic colitis; NS, not significant.

Table 2. Standardized Morbidity Ratio For Microscopic Colitis and Its Subtypes In Celiac Disease As Compared With the General Population

	SMR (95% CI)	Female, SMR (95% CI)	Male, SMR (95% CI)
Collagenous colitis	21.2 (2.7–39.8)	23.4 (2.94–43.9)	0
Lymphocytic colitis	53.7 (30.2–77.3)	47.9 (21.9–73.9)	69.2 (18.0–120.3)
Microscopic colitis	45.5 (27.7–63.3)	36.8 (19.8–54.0)	56.7 (14.7–98.7)

CI, confidence interval; SMR, standardized morbidity ratio.

compared with a United States population (Table 2). As can be seen, the relative risk of microscopic colitis in our cohort of patients with celiac disease is 45-fold that of the general population. The SMR for lymphocytic colitis was greater than that for collagenous colitis. The incidence of microscopic colitis in the Minnesota study was 6.1 cases per 100,000 person-years in men, 11.0 cases per 100,000 person-years in women;¹⁹ in comparison, the figures for those with celiac disease are: 787.6 per 100,000 person-years in women and 444.9 per 100,000 person-years in men.

Clinical Features

Among those with microscopic colitis, 64% were diagnosed with celiac disease first; the diagnosis of microscopic colitis was made because of a search for a reason for persistent diarrhea (nonresponsive celiac disease). In this group, the diagnosis of microscopic colitis was established a median of 45 months after the diagnosis of celiac disease (range 4 to 468 months). While 25% were diagnosed with both celiac disease and microscopic colitis in the same month, only 11% were diagnosed with microscopic colitis first ($P = .0001$).

Duodenal Pathology

The majority of the patients, 75%, with microscopic colitis had subtotal or total villous atrophy in duodenal biopsies, while 21% had partial villous atrophy; only a small percent had had the relatively minor Marsh I and II lesions. There was 1 patient with collagenous deposition in the duodenal biopsies (collagenous sprue).

Colonic Pathology

The majority of the patients ($n = 40$) had biopsies taken from all segments of the colon, 4 had only left-sided biopsies. Pancolitis predominated, occurring in 64%, while 16% had colitis limited to the right colon, and 20% only left-sided colitis. The majority of the patients had lymphocytic colitis (75%), while collagenous colitis was present in 25% (collagen present in biopsies from all colonic segments). Two patients had areas of collagenous colitis in biopsies taken from the right colon while the majority of their biopsies revealed lymphocytic colitis. For further analysis these 2 were included in the lymphocytic colitis group.

As shown in Table 3, a significant association was observed between microscopic colitis and the degree of villous atrophy. Individuals with microscopic colitis tended to have more severe villous atrophy (S/TVA) compared with individuals with celiac disease alone ($P < .0001$), while those with collagenous colitis had less severe villous atrophy compared with patients with lymphocytic colitis ($P < .005$). There was no association between the location and extent of colonic inflammation and degree of villous atrophy ($P = .59$). All the patients diagnosed

with microscopic colitis prior to celiac disease had collagenous colitis.

Refractory Celiac Disease

Eighteen patients in this cohort had polymerase chain reaction-based T cell receptor gene rearrangement analysis of duodenal biopsies to exclude Type II refractory celiac disease. Three patients had clonal products detected; 2 had minor bands that were not persistent in subsequent analyses. One patient had a clonal product and was classified as having Type II refractory disease. She subsequently developed an enteropathy-associated T cell lymphoma.

Clinical Follow-up

All patients were seen by an experienced dietitian who counseled the patients about a gluten-free diet, and were considered to be strictly adherent to the diet. However, the diet was inadequate for symptom control for most patients (~90%) with both celiac disease and microscopic colitis. Of those that required medication to control diarrhea, approximately 2 thirds

Table 3. Histopathologic Associations Between Degree of Villous Atrophy In Celiac Disease and Microscopic Colitis, Subtype of Microscopic Colitis, Initial Diagnosis (MC Versus CD), and Extent of Colonic Inflammation

	Marsh I-II	PVA	S/TVA	P value ^a
Celiac cohort without MC (n = 921)	1.4	49.3	49.3	.002
Microscopic colitis (n = 44)	2.4	21.4	76.2	
Subtype of microscopic colitis				
Collagenous colitis (n = 11)	10	50	40	.006
Lymphocytic colitis (n = 33)	0	12.5	87.5	
Initial diagnosis				
Celiac disease (n = 28)	0	26.9	73.1	.02
Simultaneous (n = 11)	0	0	100	
Microscopic colitis (n = 5)	20.0	40.0	40.0	
Location of colonic inflammation				
Left colon (n = 5)	0	22.2	77.8	.76
Right colon (n = 7)	0	0	100	
Pancolitis (n = 28)	3.6	25	71.4	

NOTE. All values are expressed as %.

CD, celiac disease; MC, microscopic colitis; PVA, partial villous atrophy; S/TVA, subtotal/total villous atrophy.

^aTesting the association between degree of villous atrophy in celiac disease and microscopic colitis, subtype of microscopic colitis, initial diagnosis (MC vs CD), and extent of colonic inflammation, or the equality of the probability falling into each category. The significant P values indicate that the values are not distributed equally (χ^2).

Table 4. Clinicopathologic Characteristics of Microscopic Colitis In Celiac Disease Patients

		<i>P</i> value ^a
Initial diagnosis		.0001
Celiac disease	63.6	
Simultaneous	25.0	
Microscopic colitis	11.4	
Colitis location		.0001
Left-sided	20.4	
Right-sided	15.9	
Pancolitis	63.6	
Course of MC		.008
Good response, GFD alone	4.5	
Good response, single course of therapy	27.3	
Good response, maintenance therapy	31.8	
Poor response, GFD alone	6.8	
Poor response, maintenance therapy	15.9	
Status unknown	13.6	

NOTE. All values are expressed as %. The significant *P* values indicate that the values are not distributed equally (χ^2 test).

GFD, gluten-free diet; MC, microscopic colitis.

^aTesting the equality of the probability falling into each category.

responded. The therapies used included bismuth subsalicylate (*n* = 22), mesalamine-containing drugs (*n* = 17), budesonide (*n* = 17), prednisone (*n* = 18), azathioprine (*n* = 11), and cyclosporine (*n* = 2). Of the entire cohort, 63% of the cohort ultimately required steroids (prednisone or budesonide) and/or immunosuppressants during the course of their illness. Fourteen percent were lost to follow-up.

A good response to treatment was observed in 64% of patients, though maintenance therapy with budesonide or immunosuppressants was required in 48% (Table 4). Despite maintenance medications, 16% of patients had persistent diarrhea, though were generally improved. Table 5 contains information regarding the course of treatment in our microscopic colitis cohort. Due to the combinations of treatments, logistic regres-

sion analysis to determine the relative efficacy of each treatment or different combinations of treatment was not possible. Also, certain treatments were not used in some patients, as therapies were not considered (bismuth subsalicylate) or available (budesonide) during the entire period during which this cohort was followed. It is worth noting, however, that in general, it appeared that most patients with subtotal or total villous atrophy needed steroids or other immunosuppressive drugs to control their diarrhea. It is recognized that the steroids and immunosuppressants may be active against active celiac disease in the small intestine as well as colitis.

For the entire group, irrespective of treatment, the median time to good response was 48.5 months for lymphocytic colitis (95% CI, 43.1–53.8 months) and 42 months (95% CI, 16.7–67.9 months) for collagenous colitis (*P* = .294). The median time to resolution of symptoms was 24 months (95% CI, 8.5–39.5 months) for men, and 48.5 months (95% CI, 40.4–56.7 months) for women (*P* = .326).

Follow-up Pathological Findings

We also analyzed the follow-up colonic and duodenal biopsy findings; 30 patients had follow-up duodenal, and 22 colonic, biopsies. In patients with multiple follow-up biopsies, the last biopsy was used for statistical analysis. Overall 63% of the duodenal biopsies improved over a mean period of 46 months. At follow-up 33% had PVA and 40% S/TVA. Normalization of duodenal biopsies was observed in only 4 patients. Among the follow-up colonic biopsies there was improvement in 43% over a mean time of 56 months. As shown in Table 6, there was no relationship (*P* = .26) between the direction of change (improvement versus worsening) in colonic biopsies and the direction of change in duodenal biopsies.

At the time of follow-up, of those patients with persistent diarrhea, only 30% showed improvement on their repeat duodenal biopsy, versus nearly 80% for individuals without diarrhea (*P* < .05). Although a similar trend existed for colon histopathology, the difference was not significant (*P* = .22). Persistence of diarrhea was associated with both persistent villous atrophy

Table 5. Treatments and Response to Treatment Among Microscopic Colitis in Celiac Disease

	No medication	Mesalamine/bismuth	Steroids/immunosuppressant	Mesalamine/bismuth + steroids/immunosuppressant
N	6 (13.6)	10 (22.7)	9 (20.5)	19 (43.2)
Missing in follow-up	5	3	0	3
Marsh I-II	—	—	—	1
PVA	2	—	—	1
S/TVA	3	3	—	1
Good response	1 (100)	7 (100)	8 (88.9)	10 (62.5)
Marsh I-II	—	—	—	—
PVA	—	2	1	3
S/TVA	1	5	7	7
Poor response	0	0	1 (11.1)	6 (37.5)
Marsh I-II	—	—	—	—
PVA	—	—	—	2
S/TVA	—	—	1	4

NOTE. Values are given as *n* and *n* (%). The therapies used included bismuth subsalicylate (*n* = 22), mesalamine-containing drugs (*n* = 17), budesonide (*n* = 17), prednisone (*n* = 18), azathioprine (*n* = 11), and cyclosporine (*n* = 2); 63% of the cohort ultimately required steroids (prednisone or budesonide) and/or immunosuppressants. Therapies were added sequentially. Overall response was assessed as cessation of diarrhea.

PVA, partial villous atrophy; S/TVA, subtotal/total villous atrophy.

Table 6. Relationship Between Follow-Up Duodenal Biopsy and Colonic Biopsy

Duodenal biopsy	Colonic biopsy		P value
	Improved (n = 9)	No change/worse (n = 10)	
Improved (n = 13)	7 (21.1)	6 (31.6)	.40
No change/worse (n = 6)	2 (10.5)	4 (36.8)	

NOTE. Values are expressed as n (%).

in 70% and colitis in 80%; however among those in whom the diarrhea resolved there was villous atrophy in only 20%, but persistent colitis in about 50%, suggesting that the improvement in the villous atrophy may be responsible for the clinical improvement. In addition, colitis may persist despite resolution of diarrhea.

Discussion

Our study illustrates that microscopic colitis occurred in 4.3% of a large cohort seen in a tertiary celiac disease center. All cases were diagnosed after 1990, coincident with publications about the entity in the literature appearing in the 1980s.^{7,8,20-26} The occurrence of microscopic colitis in 4.3% of our celiac cohort, however, represents a markedly increased rate of occurrence of microscopic colitis compared with a general, population based study from Olmsted County, Minnesota.¹⁹ In this analysis we only included patients seen over the same time periods. The increased risk was 45 fold and occurred in both women and men, despite both celiac disease and microscopic colitis being female predominant diseases.^{19,27} We are aware that it is difficult to compare data from population-based studies and specialty referral centers; however there are few population-based data on celiac disease within the United States. This is a major drawback to this study; however the incidence rate in the reference population we used in this study was similar (though less) in yet another North American study from Canada.¹¹ In addition, there is selection bias in our study and similar studies, because we are aware of the association of celiac disease with microscopic colitis, and it is therefore sought among the celiac disease patient population.

In the majority of our patients microscopic colitis was diagnosed after the diagnosis of celiac disease due to the occurrence of persistent diarrhea. The patients tended to be older at diagnosis of celiac disease than the celiac cohort that lacked microscopic colitis, and to have a more severe degree of villous atrophy in the duodenal biopsies. It is of interest that the diagnosis of collagenous colitis was only established in women, whereas lymphocytic colitis occurred in both sexes. The female predominance for collagenous colitis has been noted previously.^{14,19} In addition, collagenous colitis is associated with less severe pathological changes in the duodenum.

Microscopic colitis should be suspected in celiac disease when there is a poor response to a strict gluten-free diet. Several studies have demonstrated that microscopic colitis is but 1 of several conditions that need to be excluded in patients who do not respond to a strict gluten-free diet.⁴⁻⁶ Other conditions include bacterial overgrowth, pancreatic insufficiency, and refractory celiac disease.⁴⁻⁶ The latter should only be considered in those with diarrhea and persistent villous atrophy despite

adherence to a strict gluten-free diet for at least 6 months.²⁸ Patients with refractory celiac disease are further classified into Type I or Type II depending on the presence of aberrant intraepithelial lymphocytes. In Type II, the intraepithelial lymphocytes fail to express normal surface lymphocyte markers and have clonal expansion of T cell receptors.²⁹ Only 1 patient in this series fulfilled criteria for refractory celiac disease Type II, though not all were tested for the presence of aberrant intraepithelial T cells due to the lack of knowledge concerning this disorder in the earlier years of this study. The finding of microscopic colitis in the remaining patients excludes the diagnosis of refractory celiac disease (Type I) as a cause of poor response to the gluten-free diet. We did note that only 13% of the patients that had follow-up duodenal biopsies normalized their histology, though the majority improved their degree of villous atrophy. The 13% is low, even for our patients in whom we have reported that only 22% normalize.³⁰ The reason that the normalization rate is so low is unclear. Ongoing low level gluten ingestion that was not identified by us is always a possibility.

Colonoscopy should be performed in patients with celiac disease and persistent nonresponsive diarrhea. Inflammatory bowel disease may be identified;³¹ however, biopsies need to be taken irrespective of the endoscopic appearance of the colon. Biopsies need to be taken from all segments of the colon, for 16% of our cohort had colitis limited to the right colon and 20% only left-sided colitis.

Similarly, celiac disease should be considered in patients who are diagnosed with microscopic colitis,³² though this sequence of diagnosis accounted for only 11% of patients in this series. Patients who undergo both upper endoscopy and colonoscopy with biopsies as evaluation of diarrhea may receive a simultaneous diagnosis of celiac disease and microscopic colitis. The simultaneous diagnosis of both microscopic colitis and celiac disease should be undertaken with caution because intraepithelial lymphocytosis in duodenal biopsies, in the absence of villous atrophy, has been suggested in patients with microscopic colitis,³³ and colonic intraepithelial lymphocytosis, without clinical or frank lymphocytic colitis, in the setting of active celiac disease has been described.¹⁵ The latter phenomenon may be an immune overflow phenomenon from the small intestine and may improve with a gluten-free diet.

In view of a similar pathological feature of intraepithelial lymphocytosis, their increased occurrence together, and the association of microscopic colitis with more severe villous atrophy, a question arises as to whether microscopic colitis and celiac disease are etiologically related. Both entities share pathophysiological links, such as an increased likelihood of having human leukocyte antigen-DQ2,³⁴ and a similar mucosal cytokine profile, predominantly T helper-1-mediated response with elevations in interferon-gamma.³⁵ In 1 study, however, Freeman could not induce small intestinal changes in patients with microscopic colitis by adding gluten to the diet.³⁶ In addition the intraepithelial lymphocytes in both conditions are predominantly CD3+, CD8+; however, they are TCR $\gamma\delta$ + in celiac disease and TCR $\alpha\beta$ + in lymphocytic colitis.³⁷ It is unclear what causes microscopic colitis, although an abnormal response to luminal antigens has been postulated,^{37,38} and is suggested by the innate immune response in the epithelium.³⁹ The association with autoimmune diseases raises questions as

to whether microscopic colitis is in fact an associated autoimmune disease.

Several studies,⁴⁰⁻⁴³ though not all,⁴⁴ have shown that symptoms in patients with microscopic colitis respond rapidly. With relatively minor therapies, response rates of >70%, and spontaneous remission rates as high as 40% are seen.⁴³ Therapies include cholestyramine, bismuth subsalicylate,⁴⁰ and nonspecific antidiarrheal agents.⁴³ Controlled studies have shown that mesalamine and budesonide are efficacious.^{45,46} There are no controlled studies in patients with microscopic colitis and celiac disease. Our findings, however, demonstrate that steroids or immunosuppressants were required in 60% of patients seen in a specialty center, and as maintenance therapy in 50%. This suggests that the course of patients with this disease combination (nonresponsive celiac disease in whom microscopic colitis is also identified) is more difficult than those with microscopic colitis alone. Patients with collagenous colitis had a similar course to those with lymphocytic colitis. Symptoms, however, do appear to gradually resolve, even though some patients continue to use medication to control symptoms.

The pathophysiological role that small intestinal villous atrophy, compared with the colonic inflammation (colitis), shared in the cause of the diarrhea in these patients is unclear. However it was interesting that those with collagenous colitis had lesser degrees of villous atrophy in duodenal biopsies, and in those with resolution of diarrhea, pathological changes of microscopic colitis persisted more so than villous atrophy. The situation in this respect is complicated by the fact that in celiac disease, it is unclear why patients have diarrhea, for it is not correlated with the degree of villous atrophy in duodenal biopsies,⁴⁷ or with length of involvement in the small intestine as assessed by video capsule endoscopy.⁴⁸ Our findings suggest that patients with microscopic colitis and celiac disease have a difficult and protracted clinical course, requiring immunosuppressive therapy. It is possible that having both celiac disease and microscopic colitis affects the clinical course of each disorder.

Microscopic colitis should be sought in patients with celiac disease and persistent diarrhea, despite a gluten-free diet. Our study suggests that the course of these patients is complicated compared with those with either disease alone, demonstrated by a requirement for steroids or immunosuppressant therapy. Further studies are required to explore the link between these 2 conditions.

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Reprint requests

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Conflict of interest

The authors disclose no conflicts.