

BRIEF ARTICLES

Microscopic colitis: A large retrospective analysis from a health maintenance organization experience

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Abstract

AIM: To examine the demographic data on a large multi-ethnic population of patients with microscopic colitis (MC) in Southern California and to determine the association of MC with inflammatory bowel disease (IBD) and colorectal cancer.

METHODS: All patients diagnosed with MC by colonic biopsy from 1996-2005 were identified utilizing a pathology database. All biopsies were reviewed by experienced pathologists utilizing standard histologic criteria. Patients' medical records were reviewed and data regarding patient age, co-morbidities, sex, ethnicity, and medications were analyzed. An age- and sex-matched standard control group was also generated. Chi-square test was used to evaluate the associations of co-morbidities between lymphocytic colitis (LC), collagenous colitis (CC) and the control group.

RESULTS: A total of 547 cases of MC were identified,

376 patients with LC and 171 patients with CC. The female/male ratio was 3:1 in CC and 2.7:1 in LC patients. Celiac disease ($P < 0.001$), irritable bowel syndrome (IBS) ($P < 0.001$), and thyroid diseases ($P < 0.001$) were found to have a higher occurrence in MC compared to the control group. No statistical differences in the occurrence of colorectal cancer, diabetes and IBD were found between the MC group and the control group.

CONCLUSION: This is the largest group of patients with MC known to the authors that has been studied to date. Conditions such as celiac disease, IBS, and thyroid diseases were found to be related to MC. Furthermore, neither an increased risk of colorectal cancer nor IBD was associated with MC in this study.

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Key words: Collagenous colitis; Inflammatory bowel disease; Lymphocytic colitis; Microscopic colitis

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INTRODUCTION

Microscopic colitis (MC) is a condition characterized by chronic, watery diarrhea with normal endoscopic appearance of colonic mucosa, yet abnormal histology. Further classification of this condition based on histology reveals two distinct entities: collagenous colitis (CC) and lymphocytic colitis (LC). Although both entities demonstrate colonic intraepithelial lymphocytosis, increased inflammatory cells within the lamina propria and preserved crypt architecture, the presence of a

thickened sub-epithelial collagen band is characteristic of CC.

The incidence of CC is approximately 0.6-2.3/100 000 per year with a prevalence of 10-15.7/100 000, while LC has an incidence of 3.1/100 000 per year and a prevalence of 14.4/100 000^[1,2]. However, more recently published data from Olesen *et al*^[3] suggests that the incidence of microscopic colitides are on the rise. Observational studies have also suggested associations between MC and various autoimmune diseases including thyroid, rheumatoid, celiac, and inflammatory bowel disease (IBD)^[4-7]. Various medications have also been linked with MC in published case reports. Currently, little is known regarding cancer risk associated with MC.

With the number of reported cases clearly increasing, surprisingly, its etiology is still mostly unknown. Furthermore, the relationship between collagenous and LC and their association with other diseases has yet to be clearly defined. Should a connection between MC and colorectal cancer or IBD exist, this would have huge ramifications on the management of MC. Most of the currently available data on MC are from European studies with relatively small and homogeneous populations. There are even fewer comparative studies on the subtypes of MC.

The purpose of this study was to observe and report the demographic data on a large multi-ethnic population in Southern California, USA, with MC. We also report on the pattern of concurrent diseases and cancers in this group of patients.

MATERIALS AND METHODS

All patients diagnosed with MC (both collagenous and LC) from 1996 to 2005 by colonic biopsy were identified using the pathology database at Kaiser Permanente (a large health maintenance organization) in Southern California and the search words "MC, LC and CC". This region includes eight major Kaiser Permanente medical centers that serve over three million members throughout Southern California.

The histological criteria for inclusion in this study were defined as follows: (1) An increase in intraepithelial lymphocytes (more than 10 lymphocytes/100 epithelial cells); (2) Surface epithelial damage; (3) Absent or minimal crypt architectural damage; (4) An increase in sub-epithelial collagen band > 10 micrometers was required for the diagnosis of CC (Figure 1).

Experienced gastrointestinal pathologists (JM, SW, NK, RZ, MK, JP, KG) at Kaiser Permanente reviewed all biopsies.

Patients with ulcerations, erythema or any other visible abnormalities seen on the colonic mucosa during the endoscopic exam were excluded from the study. We included patients with a history of colorectal cancer.

We reviewed medical records using the Kaiser Permanente Database System and recorded data regarding patient age at diagnosis, sex, ethnicity, and concurrent medical conditions. All medications taken by patients, within 1 year prior to the diagnosis of collagenous or LC,

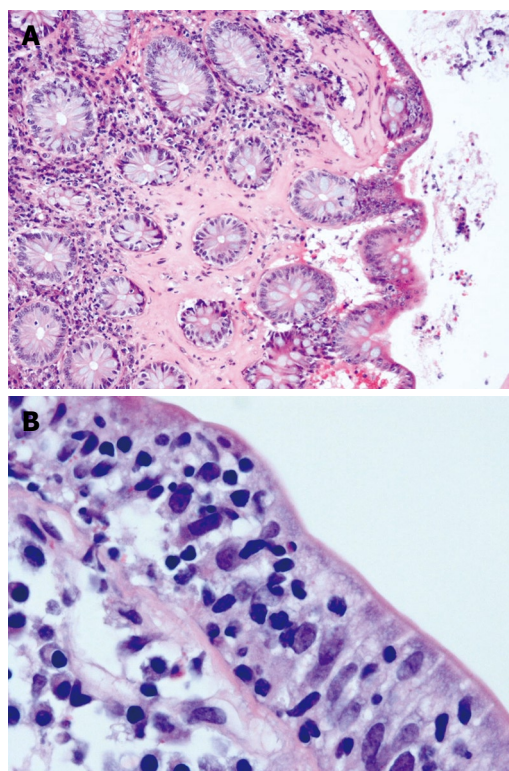


Figure 1 Collagenous colitis (A) and lymphocytic colitis (B).

were also recorded for analysis.

Demographic data such as age at diagnosis, sex and ethnicity is presented as means and standard deviation. An age- and sex-matched standard control group was also randomly generated from the same Kaiser Permanente database. We used a chi-square test to evaluate the associations of co-morbidities between LC, CC and the control group.

Differences in the clinical characteristics between LC and CC were also evaluated using the chi-square test. Differences were assumed as significant at a *P* value of less than 0.05.

The study protocol was approved by the Internal Review Board of Kaiser Permanente in Southern California.

RESULTS

From January 1996 to July 2005 a total of 547 patients were identified with MC from our database. There were 27.1% male subjects, while 72.9% were female. The average age at diagnosis was 61.7 years for both men and women. We were able to identify the ethnicity in 465 cases. The percentage of each ethnic group was as follows: 72.4% Caucasian, 6.9% Hispanic, 2.6% Asian, 2.9% African American, and 0.2% Middle Easterners.

CC

Demographics: A total of 171 patients were identified as having CC. The average age at diagnosis in these patients was 63.8 years with a standard deviation of 13.5 years. The range for age at diagnosis was between

Table 1 Comparison of our demographic data against published demographic data in collagenous colitis (mean \pm SD)

	Total number	Age at diagnosis (yr)	Gender ratio M/F
Goff <i>et al</i> ^[8] 1997	31	66	5/26
Fernandez-Banares <i>et al</i> ^[1] 1999	23	57.8 \pm 2.9	4/19
Agnarsdottir <i>et al</i> ^[9] 2002	71	66.1 \pm 14.3	8/63
Olesen <i>et al</i> ^[3] 2004	51	Not reported	6/45
Koskela <i>et al</i> ^[18] 2004	30	56.5 \pm 12.7	10/20
Kao <i>et al</i> 2006	171	63.8 \pm 13.5	42/129

29 to 93 years. The sex distribution was 24.6% male and 75.4% female. The ratio between male and female ratio was about 1:3. Of the 171 patients identified, we were able to identify the ethnicity of 152 patients. The percentage of each ethnic group was as follows: 80.7% Caucasian, 5.3% Hispanic, 2.3% African American and 0.6% Asian. No patients identified as Middle Easterners were observed^[18,9] (Table 1).

Associated diseases: Of the CC population identified, the most common endocrinopathies were as follows: hyperlipidemia (42.7%), diabetes (14%) and thyroid disease, including hyperthyroidism, hypothyroidism and Grave's disease (21%). The three most common rheumatologic and other inflammatory disorders were rheumatoid arthritis (7%), fibromyalgia (3.5%) and Raynaud/CREST syndrome (2.9%). Other diseases diagnosed in these patients included giant cell/temporal arteritis ($n = 3$, 1.75%), polymyalgia rheumatica ($n = 2$, 1.16%), systemic lupus erythematosus ($n = 1$, 0.58%) and scleroderma ($n = 1$, 0.58%). Only five patients in the CC group were diagnosed with celiac disease (2.92%). One of these patients had the diagnosis of celiac disease prior to the diagnosis of CC. Thirty patients were diagnosed with irritable bowel syndrome (IBS) prior to the diagnosis of CC, while only one patient was diagnosed with irritable bowel after the diagnosis of CC was made. We observed one patient with an established diagnosis of IBD prior to the diagnosis of CC. During a median follow up of 3 years, none of our CC patients have subsequently been diagnosed with IBD.

Compared with the control group, patients with CC had higher rates of thyroid disease ($P < 0.001$). We also observed a higher rate of celiac disease ($P < 0.01$), IBS, ($P < 0.001$) rheumatoid arthritis ($P < 0.001$) and Raynaud/CREST syndrome ($P < 0.01$) in our patients with CC (Table 2).

Cancer: The three most common cancers found in CC patients were breast ($n = 4$, 2.34%), lung ($n = 3$, 1.75%) and colorectal cancer ($n = 5$, 2.82%). Four patients were diagnosed with cancer prior to the diagnosis of CC. Only one patient was diagnosed with colorectal cancer following the diagnosis of CC. This patient was a 79-year-old female diagnosed with colorectal cancer by screening colonoscopy 5 years after the diagnosis of CC was made.

Table 2 Comparison of concurrent diseases between collagenous colitis and the control group

Disease	Number of patients affected	Percentage (%)	Compared to control group
Hyperlipidemia	73	43.5	NS
Diabetes type I and II	24	15.8	NS
Thyroid diseases ¹	36	21	$P < 0.001$
Rheumatoid arthritis	12	7	$P < 0.001$
Fibromyalgia	6	3.51	NS
Raynaud/CREST syndrome	5	2.92	$P < 0.01$
Giant cell/temporal arteritis	3	1.75	NS
Polymyalgia rheumatica	2	1.16	NS
SLE	1	0.58	NS
Scleroderma	1	0.58	NS
Celiac disease	5	2.92	$P < 0.010$
IBS	30	17.5	$P < 0.001$
IBD	1	0.58	NS

¹Thyroid diseases including hypothyroidism, hyperthyroidism and Grave's disease. SLE: Systemic lupus erythematosus.

Table 3 Comparison of our demographic data against published demographic data in lymphocytic colitis (mean \pm SD)

	Total number	Age at diagnosis (yr)	Gender ratio M/F
Fernandez-Banares <i>et al</i> ^[1] 1999	37	65.3 \pm 2.4	10/27
Agnarsdottir <i>et al</i> ^[9] 2002	54	68.7 \pm 12.7	5/45
Olesen <i>et al</i> ^[3] 2004	199	59	59/140
Koskela <i>et al</i> ^[18] 2004	54	55.4 \pm 13.2	8/46
Kao <i>et al</i> 2006	376	60.7 \pm 16.1	106/270

No cancer demonstrated a statistical difference compared with the control group, including colorectal cancer.

LC

Demographics: A total of 376 patients were identified as having LC. The average age at diagnosis in this group was 60.7 years, with a standard deviation of 16.1 years. The age range at diagnosis was between 19 to 98 years. Sex distribution was 28.1% male and 71.8% female. The ratio between men and women was about 1:2.5. Of the 376 patients identified, ethnicity was determined in 313 cases. The percentage of each ethnic group was as follows: 68.8% Caucasian, 7.71% Hispanic, 3.45% Asian, 3.19% African American and 0.26% Middle Eastern (Table 3).

Associated diseases: Of the total LC population, the most common endocrinopathies were as follows: hyperlipidemia = 44.1%, diabetes = 14.6% and thyroid disease (including hyperthyroidism, hypothyroidism and Grave's disease) = 18.8%. Rheumatoid arthritis was seen in 3.99% of the LC patients. Fibromyalgia was observed in 4.52%, while Raynaud/CREST syndrome was observed in 1.33% of the LC population. Others diseases such as giant cell/temporal arteritis ($n = 2$, 0.53%), polymyalgia rheumatica ($n = 6$, 1.6%), systemic lupus erythematosus ($n = 3$, 0.8%) and scleroderma ($n = 1$, 0.27%) were also

Table 4 Comparison of concurrent diseases between lymphocytic colitis and the control group

Disease	Number of patients affected	Percentage (%)	Compared to control group
Hyperlipidemia	166	44.10	NS
Diabetes type I and II	55	14.60	NS
Thyroid diseases ¹	71	18.80	$P < 0.01$
Rheumatoid arthritis	15	3.99	$P < 0.01$
Fibromyalgia	17	4.52	$P < 0.01$
Raynaud/CREST syndrome	5	1.33	$P < 0.01$
Giant cell/temporal arteritis	2	0.53	$P < 0.025$
Polymyalgia rheumatica	6	1.60	NS
SLE	3	0.80	$P < 0.025$
Scleroderma	1	0.27	NS
Celiac disease	13	3.46	$P < 0.001$
IBS	43	11.40	$P < 0.001$
IBD	1	0.27	NS

¹Thyroid diseases including hypothyroidism, hyperthyroidism and Grave's disease.

observed. Thirteen patients were diagnosed with celiac disease (3.46%) and six of these patients had a diagnosis of celiac disease prior to the diagnosis of LC. Forty three patients were thought to have IBS prior to the diagnosis of LC, while seven were diagnosed with IBS after the diagnosis of LC was made. Overall, 11.4% of patients with LC were diagnosed with IBS. We observed one patient with an established diagnosis of IBD prior to the diagnosis of LC. During a median follow up of 3 years, none of our LC patients have subsequently been diagnosed with IBD.

Patients with LC had a higher rate of thyroid diseases ($P < 0.01$) compared with the control group. Diseases thought to be autoimmune-related, such as rheumatoid arthritis ($P < 0.01$), Raynaud/CREST syndrome ($P < 0.01$), SLE ($P < 0.025$), fibromyalgia ($P < 0.01$), and temporal arteritis ($P < 0.025$) also had statistically higher rates of occurrence in patients with LC. IBS ($P < 0.001$) and celiac disease ($P < 0.001$) also occurred more often in patients with LC (Table 4).

Cancer: The three most common cancers found in our LC patients were breast ($n = 20$, 5.31%), prostate ($n = 7$, 1.86%) and lung ($n = 4$, 1.06%). Five patients were diagnosed with colorectal cancer prior to the diagnosis of LC. None were diagnosed with colorectal cancer after the diagnosis of LC had been made.

No cancer was noted to have a statistical difference compared with the control group, including colorectal cancer.

CC vs LC

Despite a significant population size difference, we found little statistical difference between collagenous and LC, in terms of their associated diseases. Interestingly, we found a higher rate of irritable bowel disease diagnosed concurrently with CC than with LC ($P < 0.05$).

DISCUSSION

Increasingly, MC has become more and more recognized worldwide, yet little is known about its pathophysiology and the long term outcome of the disease. Currently, multiple hypotheses exist for the pathophysiology of MC and include immune dysregulation/autoimmunity. This hypothesis is further supported by findings that human leukocyte antigen haplotype is increased in A1 and DRW53 in LC^[10]. While others have found increases in DQ2 and DQ1, three in LC and CC^[11]. Autoantibodies such as ANA have also been found to be higher in patients with MC^[12]. Indeed, multiple retrospective clinical studies have noted a higher incidence of autoimmune diseases in patients diagnosed with MC. This suspected relationship between immune dysregulation/autoimmunity and MC has led to the question of whether MC is a pre-IBD entity? If so, does the patient with MC require a higher level of surveillance and more aggressive treatment to prevent IBD from developing? These concerns were further illustrated by multiple case reports that seemed to convincingly suggest that MC may be the initial phase of a full blown IBD. However, the above theory has never been formally addressed in a large population study. In our investigation we were able to validate the previously known association between LC, CC and various autoimmune diseases, celiac disease and thyroid disorders in a large population study. Yet, interestingly, we found no significant correlation between IBD and CC/LC. Therefore, LC and CC may not be an indicator for intense surveillance to detect progression to IBD. To date, none of our LC or CC patients have been diagnosed with IBD.

Another theoretic risk for patients with MC is colorectal cancer. This concern is based on the IBD model where chronic inflammation can lead to increased dysplasia and malignancy. Thus far, to the authors' knowledge, only one study has evaluated the risk of colorectal cancer in MC. Chan *et al.*^[13] studied 117 patients diagnosed with CC during a mean follow-up period of 7 years to examine the risk of colorectal cancer. A similar risk of colorectal cancer was found in MC patients and the general population in that study. Only one patient was diagnosed with colorectal cancer after being diagnosed with MC. This was confirmed in our study as no increase in colorectal cancer occurrence was found between our patients with MC and the control group.

Interestingly, we found that IBS was associated with MC in approximately 13% of our MC patients. Other studies have also shown a correlation between IBS and MC, with IBS diagnosed in up to 23% of patients with LC^[14,15]. The relationship is unclear, however it could be due to a similar clinical presentation between MC and IBS, as suggested by Barta *et al.*^[16]. There is also increasing evidence to support an inflammatory process in the pathogenesis of IBS. Furthermore, studies have shown that increasing amounts of intraepithelial lymphocytes can be seen in patients diagnosed with post infectious

IBS^[17]. Usually, the number of lymphocytes does not reach that needed for the diagnosis of MC in most post infectious IBS patients, however, there have been cases where patients with a clinical history of post infectious IBS have been diagnosed with MC. To accurately distinguish these entities is important, as their management and treatment may be very different. For example, currently, colonoscopy is rarely performed for the diagnosis of IBS. However, as a result of our findings, colonoscopy with random biopsy may be warranted as a part of the workup for suspected diarrhea predominant IBS in the future.

Endocrinopathies such as thyroid dysfunction and diabetes have been known to have correlations with MC as noted in previously published studies. Several studies showed that diabetes was found in up to 8.3% of CC patients and in up to 13.5% of LC patients^[18,19]. Despite reports of these associations, our study did not show a statistical significance when compared with our control group. One possible explanation for this is that LC, CC and diabetes tend to occur more frequently in elderly populations and thus could easily be thought of as related diseases. In a recent published study by Williams *et al*^[20] after risk stratification of their data by age, the risk association between MC and the general population was no longer significant. Another possible explanation is that most of the previous studies were smaller in size which may have led to sampling error. However, the same argument can not be used to explain the high occurrence of thyroid dysfunction previously reported^[21]. Indeed, we found a statistically higher occurrence of thyroid dysfunction in LC and CC patients when compared to the control group. The association between thyroid dysfunction, LC and CC is still unknown, although some suggest autoimmunity as a possible cause.

There are several limitations to our study. For example, because routine screening for other disorders that may be related to MC (such as celiac disease) were not performed in a prospective format, the prevalence of these associated disorders may be underestimated. Another limitation is the lack of long term follow up. Because of this lack of long term follow up, it is possible that colorectal cancers and IBD may not have had sufficient time to manifest. Due to this, we continue to actively follow these patients and long term data should be forthcoming in the future. Another limitation involves the retrospective nature of this study for which selection bias is commonly seen. However, we hope that the large patient population would minimize such bias.

Our analysis produced many interesting observations and provoked thoughtful questions regarding the etiology, disease mechanism, and associations with other diseases and medications in the largest study to date on MC. Several of these findings have been previously noted, however, some other relationships have yet to be reported. We believe that the large number of patients in our study makes this study less vulnerable to sampling error and provides a good representation of MC.

COMMENTS

Background

The prevalence of microscopic colitis (MC) is on the rise worldwide, yet little is known about the natural history and etiology of this disease. Currently, it is believed that the disease follows a benign course; however, cases have been reported in association with inflammatory bowel disease (IBD). Its association with colorectal cancer is also poorly understood.

Research frontiers

Case reports have suggested that MC can evolve into IBD, but no studies have been carried out to thoroughly evaluate this relationship.

Innovations and breakthroughs

This is the largest study published to-date that addresses the important question of whether patients with MC have a higher prevalence of IBD compared to the general population. It also provided additional clinical information regarding this rarely-studied disease.

Applications

This study, which evaluated the largest population to-date, demonstrated that there is no increase in the incidence of IBD or colorectal cancer in patients with MC. It also showed that MC can mimic symptoms of irritable bowel syndrome which should be considered during evaluation.

Terminology

MC is a condition characterized by chronic, watery diarrhea with normal endoscopic appearance of the colonic mucosa. It is further divided into lymphocytic colitis and collagenous colitis based on its histologic appearance.

Peer review

This is an interesting paper addressing a topic which often remains scarcely investigated. The article is well balanced and the discussion is clear and exhaustive.

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