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Microscopic Colitis is Associated with Several Concomitant Diseases

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Abstract: Microscopic colitis (MC) is a disease with intestinal mucosal inflammation causing diarrhea, affecting predominantly middle-aged women. The etiology is unknown, but increased prevalence of autoimmune diseases in these patients has been described, although not compared with controls or adjusted for confounding factors. The aim of this study was to examine the prevalence of common diseases in patients with MC and controls from the general population. Hypertension, rheumatoid arthritis, asthma or bronchitis, ischemia, and diabetes mellitus were more prevalent in patients than in controls. The prevalence of gastric ulcer and cancer did not differ between the groups. Besides corticosteroids, many patients were also being treated with proton pump inhibitors, antidepressant drugs, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, statins, thyroid hormones, and beta-blockers. More patients than controls were former or current smokers (72.5% versus 57.7%). Thus, MC patients have an increased prevalence of several diseases, not only of autoimmune origin.

Keywords: concomitant diseases, drug treatments, microscopic colitis, women

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Introduction

Primary microscopic colitis (MC) is a clinical and histopathological disease of unknown etiology, characterized by chronic gastrointestinal symptoms, and a macroscopically normal or near normal colonic mucosa. The entity includes 2 basic forms: collagenous colitis (CC) and lymphocytic colitis (LC).¹ Some studies have shown a female predominance in both CC and LC,² mainly affecting middle-aged women, whereas others have not been able to confirm this in LC.^{3,4} Besides primary MC, a wide array of conditions may lead to secondary lymphocytic inflammation in the intestinal mucosa, which should be distinguished from real MC.1.

An increased prevalence of autoimmune diseases and use of anti-inflammatory drugs has been described in retrospective studies of patients with MC. On this basis autoimmunity has been suggested as an etiology.^{3,5-7} Asthma has been associated with LC, but not with CC.⁸ However, these studies have not compared the prevalence of diseases in patients with MC with controls from the general population, and no adjustment for confounding factors has been performed. Furthermore, the coexistence of autoimmune diseases and MC may be due to a high consumption of anti-inflammatory drugs, rather than a common causality.^{3,5-7} Smoking and advanced age are risk factors for developing MC, and individuals over 65 years of age are at least 5 times more likely to be diagnosed as having MC than younger individuals.^{2,9} In these women of upper middle age, it may be difficult to determine whether the MC is a primary disease, or a secondary effect due to other concomitant diseases and drug treatments influencing the colonic mucosa.¹

The aim of this cross-sectional study was to compare the prevalence of concomitant diseases in patients with MC and controls from the same geographic area, after adjustment for confounding factors.

Materials and Methods

The Ethics Committee of Lund University approved the study protocol for both patients (Dnr 2009/565 and 2011/209) and controls (Dnr 51-90). All participants gave their written informed consent to take part in the study.

Subjects

Women who had been treated for MC at any outpatient clinic of the Departments of Gastroenterology,

Skåne, between 2002 and 2010, were identified by a search for the ICD-10 classification for the 2 forms CC and LC (K52.8) in outpatient records, as well as in the local register at the Department of Pathology, Skåne University Hospital, Malmö. About 1/3 of the total number of identified patients were excluded because they were over 73 years of age, since they had many other concomitant diseases and drug therapies, obscuring the picture as to whether they were suffering from primary or secondary MC.¹ Of the patients recognized, only the 240 patients (median 63 years, range 22–73 years) who had the diagnoses verified by examination of colonic biopsies by a pathologist specialized in gastrointestinal pathology were invited to participate in the present study. Altogether, 159 (median 63 years, range 22–73 years) of the 240 patients invited accepted and were enrolled in the study. One patient was excluded due to another IBD diagnosis a few weeks after inclusion, leaving 158 patients (66%), and of these, 133 also agreed to provide blood samples. These patients represent the majority of female cases of diagnosed MC in the southernmost districts of Sweden under the age of 73 years.

Microscopic colitis is more frequent in women than in men, the small male cohort in our region being unsuitable for statistical calculations. Furthermore, as the quality of life and experience of symptoms differ between the genders,² we chose to include only women in the study.

Controls

The Malmö Diet and Cancer Study (MDCS)

The MDCS, a population-based prospective cohort study, invited all women in Malmö born 1923–1950. Recruitment was carried out between 1991 and 1996, and 41% of eligible subjects participated. In all, 17,035 women completed the baseline examination.¹⁰ The MDCS baseline examination included a dietary assessment, a self-administered questionnaire about marital status, education, employment, smoking habits, wine consumption, physical activity, medical conditions and medication, anthropometric measurements, and the collection of blood samples.¹¹ Menopausal status was defined using information on previous surgery and menstrual status. The classification of pre-, peri- and postmenopausal women has been described in detail elsewhere.¹²



Women selected as controls in a previous study on breast cancer were used in the present study as controls. In all, 737 subjects (median age 56 years, range 45–73 years) were available and the only exclusion criterion was that they should not have had a previous breast cancer at baseline.¹³

Patient recruitment and study design

Between March and June 2011, invitations including study information and the same self-administered questionnaire as was sent to the controls were sent by mail to all 240 women with MC. In addition, questionnaires about gastrointestinal symptoms, psychological well-being and Rome III criteria were sent. The patients were also invited to visit the outpatient clinics of the Departments of Gastroenterology, Skåne University Hospital, Malmö or the Central Hospital in Kristianstad, to provide blood samples. A reminding letter was sent a month after the invitation letter to those who had not answered. Questionnaires were completed 1–3 weeks before blood samples were collected. Medical records were scrutinized, and age, gastrointestinal symptoms, examinations, and treatments were recorded, as well as whether the patients had had a single attack of MC, or had persistent disease.

Patients were compared with controls from the MDSC study.

Questionnaire

A self-administered questionnaire about marital status, education, employment, smoking habits, wine consumption, medical conditions and medication was completed by both controls and patients. One of the questions was: “Have you ever been treated for any of the following diseases, namely, hypertension, rheumatoid arthritis, asthma or chronic bronchitis, gastric ulcer, ischemia including myocardial infarction, intermittent claudication and stroke, cancer, or diabetes mellitus?”.

Statistical analyses

The data were analyzed using the statistical software package SPSS for Windows® (Release 20.0; IBM, NY, USA). The patients were significantly older, with a wider age range than controls. Therefore, the 12 patients younger and the two patients older than the controls were excluded, as were patients

with celiac disease and gastroenteritis (13 patients), leaving 131 of the original 158 patients for statistical analysis. Thus, both controls and patients were within the age range 45–73 years. First, the distribution of continuous variables (age, disease duration, days of drinking wine/month) was tested using a one-sample Kolmogorov-Smirnov test. All these distributions differed significantly ($P < 0.05$) from a normal distribution. Therefore, the factors studied were categorized and values were given as median (interquartile range). There was no difference between CC and LC for any characteristics in this MC cohort¹⁴ and therefore all calculations were performed independent of the category CC or LC. The number of patients in the study cohort (131 patients) who were under treatment with a drug was given as the percentage of drug users. Differences between groups were calculated by the 2-tailed Mann–Whitney U test. Fisher’s exact test was used for categorical variables. P -values < 0.05 were considered statistically significant.

Age was divided into 5-year intervals. The cohort was divided into quartiles of the number of days wine was taken per month. Smoking was divided into 3 categories: subjects who had never smoked, subjects who had stopped smoking, and current smokers, including both regular and occasional smokers. Employment was divided into 3 categories: employed, retired, or others, where others included housewives, students, and unemployed. Education was divided into patients with or without a university education. Some answers concerning days of drinking wine/month and level of education were lacking. These were labeled as separate categories. Factors intended to be studied (independent variables) were initially examined using univariate analyses to calculate odds ratios with 95% confidence intervals (OR with 95% CI). Analyses were then adjusted for age at baseline, smoking, the number of days of drinking wine/month, level of education, and employment, as these characteristics differed by >5 percentage points between controls and patients.

Results

Patient characteristics

In total, 131 women (median age 63 (59–67) years) with MC were included in the statistical calculations (Table 1). Collagenous colitis was diagnosed in 82 patients (62.6%) and LC in 49 patients (37.4%).

**Table 1.** Patient and control characteristics.

	Controls n = 737	Microscopic colitis n = 131
Age at study (years)	56.16 (50.47–62.36)	63.00 (58.94–67.15)
Age groups (%)		
45–49	17.1	4.6
50–54	22.3	6.9
55–59	22.3	13.7
60–64	19.5	32.1
65–69	11.7	26.0
70–74	7.2	16.8
Smoking habits (%)		
Never smoked	42.3	27.5
Stopped smoking	29.9	36.6
Current smokers	27.8	35.9
Days of drinking wine/month (%)		
Missing data	6.8	5.3
0–2	49.5	42.7
3–4	15.2	12.2
5–7	12.3	8.4
>7	16.1	31.3
Married women (%)	61.9	58.0
Level of education (%)		
Missing	0	2.3
≤12 years at school	76.1	67.9
>12 years at school	23.9	29.8
Employment (%)		
Employed	65.7	44.3
Retired	26.5	49.6
Others*	7.9	6.1

Notes: *Includes housewives, students and unemployed. Values are given as median (interquartile range).

The duration of the disease was 7 (3–14) years. Measurements of hemoglobin (Hb) in blood and C-reactive protein (CRP) in plasma were in the majority of patients within reference values, showing that the patients were in an overall inactive phase (data not shown). Of the patients, 91.7% were born in Sweden compared with 90.2% of the controls. More patients than controls had completed a University degree ($P = 0.001$). As the patients were older than the controls, more patients were retired ($P < 0.001$) (Table 1).

Smoking and drinking habits

There were more controls than patients who had never smoked, and the prevalence of both current and former smokers was higher among the patients (Table 1). More patients than controls drank wine >7 days a month (Table 1).

Concomitant diseases

The presence of any concomitant disease was more prevalent in patients with MC (58.8%) than in controls (35.5%) (adjusted OR = 1.81, 95% CI = 1.18–2.81). Hypertension was present in more than 1/3 of the patients. Rheumatoid arthritis was 6 times more common and asthma and bronchitis 3 times as common in patients as in controls (Table 2). The type of diabetes mellitus is not known in controls, but 2 of the patients with MC had type 1 diabetes and 7 had type 2 diabetes. There was no difference between those who had had a single attack of MC or a persistent MC in those with concomitant diseases and those without ($P = 0.930$). There was no difference in duration of MC, or age at inclusion, between those with concomitant diseases and those without in addition to the MC ($P = 0.564$ and $P = 0.146$, respectively).

The patients were currently being treated with several drugs at the time of inclusion. The most common drug treatments as a percentage of the study cohort were corticosteroids (32.1%), proton pump inhibitors (26.0%), antidepressant drugs, specifically selective serotonin reuptake inhibitors (21.4%), angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (18.3%), statins (17.6%), thyroid hormones (17.6%), and beta-blockers (16.0%). Patients on any of these drug treatments were older at inclusion (64.92 (60.00–68.34) years and 62.07 (55.55–64.24) years, respectively, $P = 0.012$). Those who had persistent MC had a higher prevalence of current drug treatment ($P = 0.024$). 8 of the 31 patients with rheumatoid arthritis used non-steroidal anti-inflammatory drugs as well as many other drugs. There was no difference in the prevalence of CC and LC in patients who were on any of these drugs or had any of the concomitant diseases ($P = 1.000$ and $P = 0.931$, respectively).

Discussion

In spite of excluding all those over 73 years of age, to get a fairly healthy group with real MC, several concomitant diseases and drugs were still present. All chronic diseases measured were over-represented in patients, in contrast to a history of gastric ulcer or cancer.

Previous studies have been retrospective, collecting patient cohorts seen at tertiary centers.^{5–7} In our present study, we used a cross-sectional design,

**Table 2.** The prevalence of different diseases in microscopic colitis (MC) and controls.

	Controls n = 737	MC n = 131	Crude OR 95% CI	OR 95% CI
Hypertension (%)				
Missing	8.4	1.5	–	–
No hypertension	77.7	62.6	1.00	1.00
Hypertension	13.8	35.9	3.22 (2.12–4.88)	2.73 (1.49–3.78)
Rheumatoid arthritis (%)				
Missing	8.4	1.5	–	–
No rheumatoid arthritis	87.9	74.0	1.00	1.00
Rheumatoid arthritis	3.7	23.7	7.67 (4.39–13.40)	7.21 (3.81–13.64)
Asthma and bronchitis (%)				
Missing	8.4	1.5	–	–
No asthma	85.5	80.9	1.00	1.00
Asthma	6.0	16.8	2.97 (1.71–5.16)	3.18 (1.68–6.00)
Cancer (%)				
Missing	8.4	1.5	–	–
No cancer	85.9	89.3	1.00	1.00
Cancer	5.7	8.4	1.42 (0.71–2.83)	1.14 (0.53–2.47)
Diabetes mellitus (%)				
Missing	8.4	1.5	–	–
No diabetes mellitus	90.5	90.8	1.00	1.00
Diabetes mellitus	1.1	6.9	6.31 (2.38–16.67)	4.91 (1.62–14.87)
Gastric ulcer (%)				
Missing	8.4	1.5	–	–
No gastric ulcer	84.3	80.9	1.00	1.00
Gastric ulcer	7.3	16.8	2.39 (1.40–4.08)	1.77 (0.95–3.30)
Ischemia* (%)				
Missing	8.4	1.5	–	–
No ischemia	88.7	88.5	1.00	1.00
Ischemia	2.8	9.9	3.49 (1.70–7.16)	2.96 (1.30–6.76)

Notes: *Including myocardial infarction, intermittent claudication and stroke. Analyses were performed adjusted for age at baseline, smoking, days of drinking wine/month, level of education, and employment, as these characteristics differed by >5 percentage between controls and patients.

Abbreviations: OR, Odds ratio; CI, Confidence interval.

collecting patients from the whole region at primary, secondary and tertiary centers. This approach reflects the patient group in a better way, as patients handled at tertiary centers are often selected cases.¹⁵ As patients with MC are women of upper middle age with former or current smoking in the anamnesis, it is to be expected that asthma, bronchitis, and cardiovascular diseases will be frequently seen in such a cohort, apart from diseases of autoimmune origin. In the present study, hypertension was the most common concomitant disease, and recent research confirms that smokers have a higher prevalence of hypertension than non-smokers.¹⁶ A high prevalence of cardiovascular diseases in patients with MC has been described previously, but this was not compared with a control population.¹⁷

The medication of the controls is not reported here because drug recommendations have been

changed since the control cohort was recruited. However, medication in controls should be less than of the patients as they were healthier. In accordance with previous reports,¹⁸ the present patients who were taking drugs were older than un-treated ones. It has been suggested in previous studies that the drugs being consumed extensively by the patient group are associated with MC and could explain the persistent character of the disease.^{6,18–20} The consensus is that drugs suspected to induce MC should be withdrawn prior to diagnosis, and that the introduction of treatment against MC may not be followed in the daily clinic.² This could contribute to the high prevalence figures of MC in the growing elderly population, with more efficient treatment regimens for cardiovascular diseases.² Prospective studies are needed to determine whether the introduction of a new drug precedes the development of the disease, and whether the disease



remains resolved after drug withdrawal, in order to estimate appropriate prevalence figures of MC.

Ischemic colitis is another frequently diagnosed condition in elderly patients with a history of smoking, cardiovascular diseases and diabetes mellitus, and in those who are on vasoactive drugs.²¹ These characteristics are similar to those described for the MC population.^{2,3,5} Corticosteroids are used in the treatment of MC, with a better response than anti-inflammatory drugs, and corticosteroids can also be useful in the treatment of ischemic, radiatic, and toxic colitis.^{2,21–23}

There are several limitations in this study. One is the use of an external control group, and that recommendations for drug prescription have been changed since our recruitment of controls. It is very difficult to recruit healthy volunteers to clinical studies. The response rate of our control group was 41%, and it is possible that these subjects are healthier than those who did not agree to participate. However, it is a strength of the study to, for the first time, compare patients with MC to such a well-defined control group.¹³ Furthermore, the data concerning smoking, overweight status, and level of education were similar in this control group to a study with 80% participation from the same population.¹⁰ We could not find from the medical records whether MC was developed prior to or after the introduction of new drugs, and therefore it is impossible to determine whether the disease is primary or secondary. An additional strength of the study was that the control group is derived from the same geographic area as the patient group, and that calculations are adjusted for age differences, life style factors, and socioeconomic factors.

In conclusion, patients with a diagnosis of MC are a selection of middle-aged women, former or current smokers, with several concomitant diseases and cardiovascular ageing, and therefore are under treatment with a wide range of diverse drugs. It is not surprising that these patients exhibit gastrointestinal symptoms and microscopic, intestinal, mucosal inflammation. These changes must be interpreted with caution, before considering them as a separate entity of autoimmune origin, instead of secondary reactions to ischemia and toxic stimulants. Efforts must be made to better classify and diagnose patients with real, primary MC, to avoid over-prescription of corticosteroids.

Author Contributions

Conceived and designed the experiments: BR, JM, BO. Analyzed the data: BO. Wrote the first draft of the manuscript: BO. Contributed to the writing of the manuscript: BR, JM, BO. Agree with manuscript results and conclusions: BR, JM, BO. Jointly developed the structure and arguments for the paper: BR, JM, BO. Made critical revisions and approved final version: BR, JM, BO. All authors reviewed and approved of the final manuscript.

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Competing Interests

Authors disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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