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Prevalence and predictive factors of microscopic colitis in patients with chronic watery non-bloody diarrhea: A tertiary center study

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ABSTRACT

Microscopic colitis (MC) is increasingly recognized during colonoscopy and biopsy of normal mucosa in chronic watery non-bloody diarrhea (CWND) patients. The prevalence and predictive factors of MC among CWND patients with normal colonoscopy were

investigated in this study. 194 patients with CWND of unknown etiology in the period from March 2017 to June 2018 underwent full colonoscopy and biopsy. A total of 88 with normal colonoscopic findings were enrolled in this study and pathology results analyzed. The study showed that 8/88 (9.1%) patients with CWND and normal colonoscopy had MC; all of MC patients had lymphocytic colitis (100%). Predictive factors for MC were the age ≥50 years, frequent diarrhea>7 motions/day, duration of diarrhea ≤6 months, nocturnal diarrhea, abdominal pain, weight loss, current use of PPI and/or H_2 receptors blockers and low serum Na and/or K level. We have created a diagnostic scoring system for the prediction of MC, with ranging scores from −1 to +10. A cutoff value >3 recognized MC patients with 100% sensitivity and 91% specificity (AUC, 0.99). With scores >5 and >6, specificity increased to 97% and 100% while the sensitivity decreased to 75% and 62% respectively (AUC, 0.99). Hence, this study concluded that MC is not uncommon in CWND patients and normal colonoscopic findings. A biopsy of normal colonic mucosa is emphasized to reach the definite diagnosis of MC. However, the created scoring system can identify MC patients and lower costs by recognizing unlikely MC patients.

Keywords: Microscopic colitis, lymphocytic colitis, chronic watery diarrhea, predictive factors, scoring system.

1. INTRODUCTION

Microscopic colitis (MC) is a type of colonic inflammatory disease leading to chronic watery non-bloody diarrhea (CWND). Approximately 10% of chronic diarrhea patients have MC and its incidence varies between 3.7% and 13% (Datta et al., 2009). In patients with MC, the colon has a normal appearance during a colonoscopic examination. The diagnosis is instituted by colonic mucosal biopsy. There are two main subtypes of MC; lymphocytic colitis (LC) and collagenous colitis (CC). LC denotes increase intraepithelial lymphocytosis while CC is diagnosed by an increased thickness of the subepithelial collagen band (Pektas et al., 2018). It typically occurs in middle-aged and elderly patients and has a female preponderance. The median age for CC diagnoses was 64.9 (range, 57.03– 72.78) years and 62.18 (range, 53.99–70.38) years for LC (Tong et al., 2015). Increasing clinician awareness of MC leads to increase diagnosis.

Established risk factors for MC are female sex, higher age, associated autoimmune diseases like thyroid disease or celiac disease, past or recent diagnosis of malignancy, and a history of solid organ transplants (Storr, 2013). Aim of this study is to estimate the prevalence of MC in CWND patients and to identify the predictive factors associated with MC.

2. PATIENTS AND METHODS

Patients and study setting

All consecutive adult patients presented to our center with CWND (defined by persistent symptom for at least 4 weeks) in the period from March 2017 to June 2018 underwent a full colonoscopy. Department of gastroenterology in the hospital is a referral center for diarrheal illness in the area. Around 2200 colonoscopies /year are performed.

All patients with infectious diarrhea evident in stool examinations or any other known intestinal pathology were excluded. Additionally, patients who tested positive for HIV, and patients with comorbidities or contraindication for colonoscopy were not included in this study. Only patients with normal colonoscopy who fulfilled the previous criteria were enrolled in the study. Only patients with normal colonoscopy who fulfilled the previous criteria were enrolled in the study. Celiac disease (CD) prevalence was investigated by serological CD-related antibodies (Immunoglobulin A (IgA) tissue trans-glutaminase antibodies (tTG) and total serum IgA level) and by reviewing histopathology of duodenal biopsies.

Data Collection

From all patients, after given informed consent, Demographic and clinical data were prospectively collected before colonoscopy. Relevant demographic data included the patient's age at the enrollment`s time, smoking, gender, and use of any medications that have a role in the etiology of MC (e.g. PPIs, NSAIDs, H_2 receptors blockers, statins, lisinopril or SSRIs) (Beaugerie and Pardi, 2005). Symptoms data include information about stool consistency, the daily number of motions, nocturnal symptoms and duration of diarrhea, other symptoms such as abdominal pain, vomiting, anorexia, loss of weight, fever, history of autoimmune diseases and history of other systems affection.

Routine labs (blood sugar, complete blood count (CBC), Erythrocyte sedimentation rate (ESR), kidney function test (KFT), liver function test (LFT), serum sodium (Na) and potassium (K), thyroid function test, and celiac serology). Fresh Stool specimens for microbiological and parasitological examinations, culture, and serology for clostridium difficile toxin in the stool were collected prospectively from all patients. An abdominal ultrasound was done for all patients.

Colonoscopy and biopsy sampling procedure

Complete colonoscopy has been done for all patients. They were prepared according to the method agreed by the gastrointestinal endoscopy center. The adopted method in this center is to stop solid foods a day before the examination (only clear liquids on the day of the preparation; the day before a colonoscopy). Preparation was administered as a split-dose. The procedure has been carried out under deep sedation in the majority of patients, and some patients underwent the procedure under conscious sedation.

During the colonoscopy, random multiple biopsies were taken using a standard, open-type endoscopic biopsy forceps from endoscopically normal-appearing mucosa at different colonic segments, at least two biopsies were taken from each colonic segment; right, transverse, descending and the sigmoid colon (Yantiss and Odze, 2009). They were immediately placed in bottles with a 10% formalin solution and sent for processing in the pathology department at the same hospital.

Histopathological diagnostic criteria for MC

Slides of processed biopsy specimens were stained with Hematoxylin and Eosin (H and E) and Masson's trichrome dyes. Diagnostic criteria for MC include increase chronic inflammatory infiltrates in the lamina propria, increase colonic intraepithelial lymphocytes (IELs), surface epithelium degeneration, and increase cryptal mitosis. More than 20 IELs /100 epithelial cells in the crypts (normal <1-5/100) are required for LC diagnosis. In the case of CC, the thickness of the collagen band in the subepithelium measured by an ocular micrometer in specimens stained with Masson's Trichrome should be >10µm to be diagnosed (Erdem et al., 2008).

Incomplete MC (MCi) comprises patients with biopsies that don't fulfill the histological criteria specific for LC and CC but have clinical features of MC. In which there is lamina propria inflammatory infiltrates and slightly increased collagenous band thickness >5 but <10µm in case of incomplete collagenous colitis (CCi) or the number of IELs >10 and <20 in case of incomplete Lymphocytic colitis (LCi) (Chang et al., 2005).

Statistical analysis

Data obtained were analyzed statistically using the statistical package for the Social Sciences (SPSS) program version 25 (SPSS Inc., Chicago, IL). Data were summarized using mean ± standard deviation (SD) and median for quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test (Chan, 2003a). For comparing categorical data, Chi-square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 (Chan, 2003b). The associations between the data and the presence of MC were evaluated by univariate logistic regression and expressed as odds ratios (ORs) with a 95% confidence interval (CI). Variables showed statistically significant univariate ORs were used in the MC predictive diagnostic scoring system (Kane et al., 2015).

Regression coefficients of the statistically significant predictors using univariate analysis were converted into assigned item scores by dividing with the smallest coefficient (1.761) and rounding up to the nearest integer. A total score formulated by summation of the individual item scores. The best cut-off value of the score for the diagnosis of MC was made by analysis of the area under the curve (AUC). Statistical significant was considered when P values <0.05. As described by *(Galen, 1980)* the diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic efficacy were also calculated (Galen, 1980).

3. RESULTS

In this study, 194 patients underwent colonoscopy for the indication of CWND with no apparent cause from March 2017 to June 2018. Of the total number of patients only 88 who have normal mucosa during colonoscopy were included in the study, 41(46.6%) females and 47 (53.4%) males. The mean age of the patients is 38.03 years (age range: 15-72years).

Liquid or loose stool was present in all patients. No ova, cysts, or parasites detected in the stool analysis, and the stool culture also did not yield any pathogens. Colonoscopies were macroscopically normal. The intubation of the terminal ileum was achieved in 88 (100%) patients and it was normal in all patients.

Pathological diagnosis of MC was made in 8 (9.1%); All cases were LC (figure 1), other biopsies revealed non-specific colitis in 54 (61.4%) patients (figure 2), normal histology in 21 (23.9%) patients (figure 3), MCi in 3 (3.4%) patients, eosinophilic colitis and IBD in 1 (1.1%) patient for each.

Demographic and clinical features of the studied patients

Demographic features (gender, age); smoking and family history as well as important clinical data of patients with histopathological diagnoses of MC were analyzed and were compared with patients with non-specific and normal histopathology (non-MC control

group, 75 patients) (Table 1). Patients with MC were significantly older (48.75 ± 8.88 years) than non-MC patients (37.20 ± 12.77 years) (P= 0.012) and age ≥50 years showed statistically significant correlation with MC (P= 0.011).

Important clinical data analysis, showed a statistically significant correlation regarding the duration of diarrhea ≤6 months (P= 0.001), abdominal pain (P= 0.032), nocturnal diarrhea (P= 0.003), and weight loss (P= 0.003) with the diagnosis of MC.

Two patients with specific diagnosis (IBD and eosinophilic colitis) as well as three MCi patients which is not yet classified as one of the main types of MC were excluded from the control group; non-MC group). There was a statistically significant correlation regarding current drug intake; PPI (P= 0.002) and H_2 receptor antagonists (P= 0.001) intake with the diagnosis of MC whereas no statically significant differences found with other drugs (Table 2).

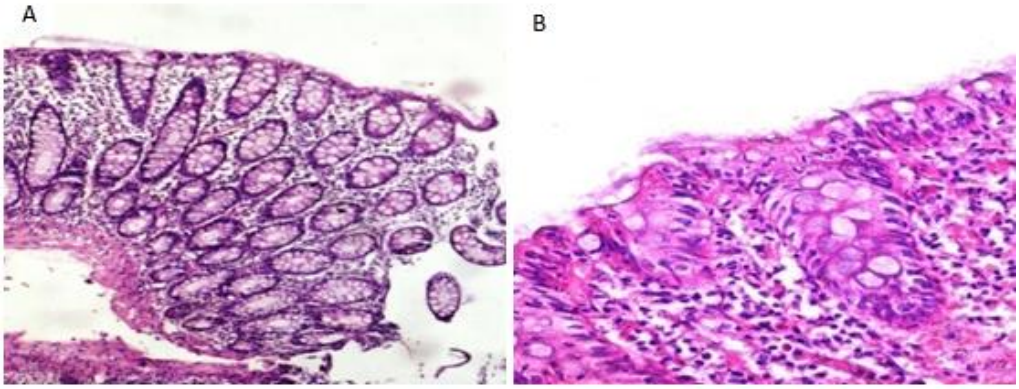

Figure 1 Lymphocytic colitis: A) H & E stained slide 100 X view showing increase number of intraepithelial lymphocytes with inflammatory hypercellularity in the lamina propria. B) high power H & E stained slide 400 X view showing increased intraepithelial lymphocytes and degenerative changes in the surface epithelium.

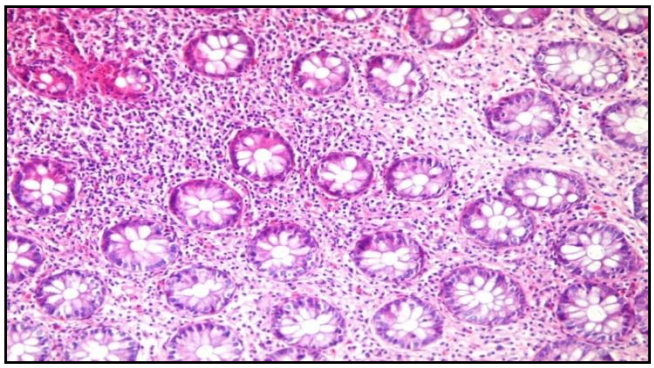

Figure 2 Chronic non specific colitis (H & E stained slide 200 X view)

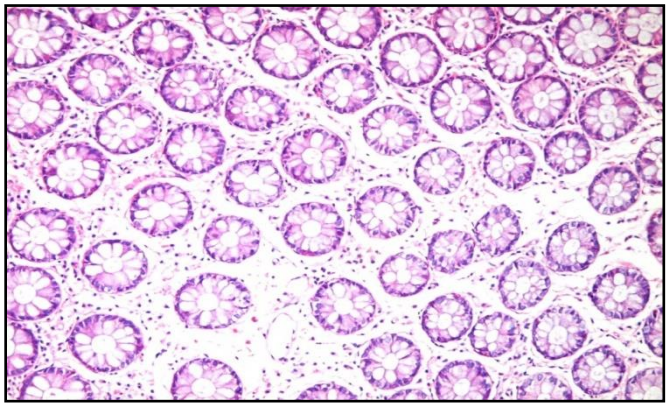

Figure 3 Normal colonic mucosa (H & E stained slide 200 X view)

Table 1 Demographic and clinical data of the studied patient groups (MC and non-MC).

		MC (n=8)		Non-MC (n=75)		P value
		Count	%	Count	%	
Gender	Male	2	25	41	54.7	0.147
	Female	6	75	34	45.3	
Age (mean ±SD)		48.75 ± 8.88		37.20 ± 12.77		0.012
(Age ≥ 50)		5	62.5	13	17.3	0.011
Smoking		1	12.5	22	29.3	0.434
Family History		0	0	5	6.7	1
Duration of diarrhea						
≤ 6months		6	75	10	13.3	0.001
> 6 months		2	25	65	86.7	
Abdominal pain		4	50	64	85.3	0.032
Nocturnal diarrhea		5	62.5	9	12.0	0.003
Weight loss		6	75	15	20	0.003
Vomiting		1	12.5	16	21.3	1
Tenesmus		2	25	6	8	0.170
Anorexia		0	0	2	2.7	1
Fever		3	37.5	8	10.7	0.068
Stool incontinence		1	12.5	1	1.3	0.185
Bowel motion frequency/day (Mean ± SD)		8.50 ± 2.07		5.53 ±1.69		< 0.001

SD=stander deviation

Table 2 The current drugs used in the studied patients (MC and non-MC)

	MC (n=8)		Non-MC (n=75)		P value
	Count	%	Count	%	
Current Drug intake	7	87.5	40	53.3	0.129
NSAID	2	25	9	12	0.286
Aspirin	1	12.5	4	5.3	0.406
PPI	6	75	14	18.7	0.002
H_2 receptor antagonists	7	87.5	12	16	< 0.001
Lisinopril	0	0	1	1.3	1
Statins	0	0	2	2.7	1

The laboratory investigations in relation to microscopic colitis

There was no statistically significant difference regarding elevated inflammatory markers, presence of anemia or other routine labs in patients with MC and control group except for the low serum Na and K levels, as lower levels were correlated significantly with MC patients (P= 0.038 and 0.009, respectively) when compared to control group. Thyroid dysfunction and celiac disease were diagnosed

in 2 (25%) and 1 (12.5%) patients with MC respectively and in 4 (5.3%) and 2(2.7%) patients in the control group respectively with a non-significant P-value (Table 3).

Table 3 The laboratory investigations of the MC and non-MC patient`s groups.

		MC (n=8)		Non MC (n=75)		P value
		Count	%	Count	%	
Anemia		5	62.5	42	56	1
Leukocytosis		0	0%	4	5.3%	1
Low Platelets		0	0%	3	4.0%	1
Inflammatory markers (ESR)	Elevated	4	50	27	36	0.464
FBS level	Elevated	1	12.5	11	14.7	1
Bilirubin	Elevated	1	12.5%	6	8.0%	1
ALT	Elevated	1	12.5%	23	30.7%	0.522
AST	Elevated	0	0%	18	24	0.428
ALP	Elevated	0	0%	4	5.3	0.191
Serum Albumin	Low	3	37.5	27	36	1
Renal impairment (↑Urea & Cr)		3	37.5	12	16	0.153
Serum Na level	Low	3	37.5	6	8	0.038
Serum K level	Low	4	50	7	9.3	0.009
Thyroid abnormalities (TSH level)	Low	2	25	3	4	0.101
	Elevated	0	0	1	1.3	
SEROLOGICAL TESTS						
ANA	High	1	12.5	1	1.3	0.185
celiac serology	Elevated	1	12.5	2	2.7	0.265

ESR: Erythrocyte Sedimentation Rates; FBS: Fasting Blood Sugar; Cr: Creatine; Na: Sodium; K: Potassium; TSH: Thyroid Stimulating Hormone; ANA: Anti-Nuclear Antibody.

Multivariable logistic regression analysis of microscopic colitis

Analysis using multivariate logistic regression showed that diagnosis at the age≥50 years, frequency of bowel motions >7 /day, duration of diarrhea≤6 months, nocturnal diarrhea, loss of weight, abdominal pain, and current use of PPI and / or H_2 receptors antagonist were associated with the diagnosis of MC (Table 4).

Table 4 Scoring system for predicting MC in Patients with CWND

	Item	regression coefficient	P- value	OR	95% C.I. Lower	95% C.I. Upper	Item score
MICROSCOPIC COLITIS	Duration of diarrhea ≤ 6 months	2.970	0.001	19.500	3.446	110.353	2
	Age ≥ 50	2.073	0.009	7.949	1.685	37.495	1
	Bowel motion frequency > 7/day	2.860	0.001	17.455	3.115	97.811	2
	Serum Na and/or K	2.125	0.008	8.375	1.746	40.170	1
	PPI and/or H_2 receptor antagonist	3.173	0.004	23.882	2.744	207.895	2
	Abdominal pain	-1.761	0.024	0.172	0.037	0.791	-1
	Nocturnal diarrhea	2.503	0.002	12.222	2.488	60.042	1
	Weight loss	2.485	0.004	12	2.198	65.515	1

Microscopic colitis scoring system

A scoring system using these factors was made with weighted points assigned according to the strength of correlation (Table 4). Predicting MC patients was made when a cut of value > 3 points in the scoring system was used with 100% sensitivity and 91 % specificity (AUC, 0.99). Specificity increased to 97% and 100% while the sensitivity decrease to %75 and % 62 when a score > 5 and > 6 was used respectively (Table 5) and (figure 4).

Table 5 The diagnostic performance of the MC scoring system

AUC	95% CI	*P*-value	Cutoff	SN	SP	PPV	NPV	Accuracy
0.99	0.98-0.100	0.001	>3	1.00	0.91	0.53	1.00	0.92
			>5	0.75	0.97	0.75	0.97	0.95
			>6	0.62	1.00	1.00	0.96	0.96

AUC: Area Under ROC Curve, CI: Confidence Interval, SN: Sensitivity, SP: Specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value.

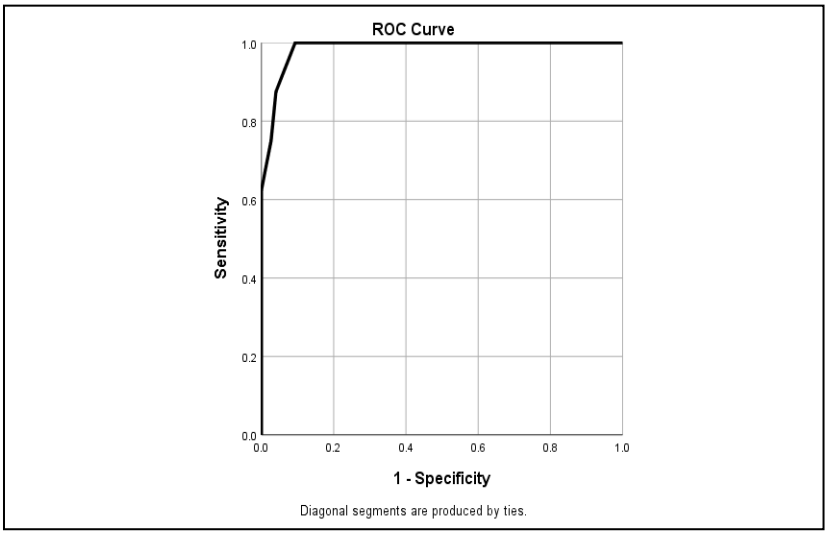

Figure 4 Receiver Operating Characteristic (ROC) Curve of the microscopic colitis prediction score

4. DISCUSSION

This study demonstrates that microscopic colitis is quite not an uncommon cause of CWND of unknown etiology in our country. From a total of 88 patients with CWND and normal colonoscopy, 8 (9.1%) patients had MC and all patients were LC. A previous retrospective study was done in by Gado and his colleagues (2011) on 44 subjects with chronic watery diarrhea and normal colonoscopy found that 22 (50%) had MC (Gado et al., 2011), which is nearly similar to the high prevalence rates reported in other developing countries such as Peru (40%) (Valle Mansilla et al., 2002) and Tunis (29.3%) (Essid et al., 2005). According to recent meta-analysis mostly from the developed Western world, the overall annual incidence of LC is 4.85/100,000 person-years and 4.14/100,000 person-years for CC. The overall prevalence of LC is 63.05 cases/ 100,000 person-years and 49.21 cases/ 100,000 person-years for CC (Tong et al., 2015).

In our study, the gender distribution of MC patients showed high females to males ratio, which is similar to the previously published studies that found an increased female to male incidence ratio for LC (1.92) and CC (3.05) (Tong et al., 2015). Diagnosis of MC can be done in patients of any age, however, the elderly are more commonly affected as described in the previously published studies (Tong et al., 2015). In our study, the mean age at diagnosis was 48.75 years (ranges from 34 to 59 years). Our result was consistent with Park et al. prospective study in Korea on patients with CWND that found the mean age of MC was 47.5 years (Park et al., 2011). However, previous studies demonstrated that patients with LC were slightly younger in comparison to CC in which the mean patients' age of LC and CC were between 53.99-70.38 years, and 57.03-72.78 years, respectively (Tong et al., 2015).

In this study, the median duration of the disease was 8.5 (4-24) months. However, the duration of diarrhea in the majority of patients with LC (75% of patients), in our study, was ≤ 6 months. A retrospective analysis of 199 patients with CWND reported a

median of 5 (3-12) months disease duration in LC patients until treatment (Olesen et al., 2004), another study by Bjørnbak et al. reported a median of 4 (2.5-4) months duration until the diagnosis of LC (Bjørnbak et al., 2011). The symptoms presentation of both LC and CC is similar (Storr, 2013). All patients in this study complained of CWND. Nocturnal diarrhea, weight loss, and abdominal pain were frequently encountered in patients with MC. These findings were consistent with the previous largest retrospective study (Olesen et al., 2004). Tenesmus and fever were less frequent, vomiting and stool incontinence were extremely rare and anorexia was absent in all MC patients in our study. MC etiology still unknown, but many risk factors were identified as; inflammatory or immune response to luminal antigens, autoimmunity, and drugs (NSAIDs, PPI, ranitidine, carbamazepine, simvastatin, ticlopidine, flutamide, etc.), (Macaigne et al., 2014). Also, geographical distribution differences could be explained by exposure to different risk factors (Roth et al., 2014). There is a controversy regarding the association between drug intake and the development of MC. Some argue that MC may result in an insult to the colon causing symptoms to present faster whereas some believe that medications are causal factors (Bonderup et al., 2018).

In our study, the majority of patients were consuming drugs (87.5% in the MC group and 53.3% in the control group, p=not significant). A similar result was demonstrated by Guagnozzi et al., who found that the majority of patients had been prescribed at least one medication during the year before the colonoscopy (71.7% in the MC group and 67.8% in the control group, p = not significant) (Guagnozzi et al., 2015). It is known that PPIs, H_2 receptor antagonists, and NSAIDs medications can affect the permeability of intestine which allow antigens to travel into the lamina propria and may lead to an immune reaction resulting in a lymphocytosis (Mullin et al., 2008), or by modifying the intestinal microbiota composition (Imhann et al., 2016).

In our study, we observed a strong association between current PPI intakes among MC patients. This finding was consistent with the previous largest retrospective study by Bonderup et al. (2018) conducted on 10652 patients diagnosed for first-time with MC [6254 (59%) with CC and 4398 (41%) with LC], that demonstrated a strong association between MC and current use of PPI (OR 6.98; 95% CI: 6.45-7.55) (Bonderup et al., 2018). Also, in our study, we observed a significant association between the current intakes of H_2 receptor antagonists among MC patients. In a case-control study on 1211 MC patients and 6041 matched controls done by Verhaegh et al. showed H_2 receptor antagonist medications involve in risk increasing of MC (OR 2.40; 95% CI: 1.73–3.31) (Verhaegh et al., 2016). NSAIDs and aspirin were used by 25% and 12.5% of our MC patients respectively, with no statistical differences as compared to the control group. Previous studies reported that exposure to NSAIDs including aspirin linked to risk increasing of MC (Park et al., 2011), however, this association in other similarly designed studies have not been universally reproduced. Gado et al., 2011 reported that their patients diagnosed with MC had no previous history of NSAIDs (Gado et al., 2011).

In our study, smoking was not statistically significant between MC patients as compared to the control group. These data are even more convincing if one considers the sex differences and type of MC in these patients as the majority of our patients were females and current smoking reported to be more correlated with CC than LC (Baert et al., 1999). Microscopic colitis has also been associated with several other diseases with an autoimmune background (e.g., autoimmune thyroiditis, type 1 DM, and non-erosive oligoarticular arthritis) (Macaigne et al., 2014). Whether these associations reflect the autoimmune pathogenesis of MC is unclear. In one report, concomitant autoimmune diseases were more common in patients with CC as compared with LC (Koskela et al., 2004). Celiac disease is reported to be associated with12.9% MC patients (Vigren et al., 2013).

In our study, the autoimmune marker; ANA was positive in one MC patient (12.5%) and one non-MC patient (1.3%). Celiac serology with tTG-IgA was positive in one MC patient (12.5%) and 2 patients (2.6%) with non-MC but there was no significant statistical difference between the two patients groups, thyroid dysfunction (evident by abnormal TSH level) was observed in two MC patients (25%) and 4 non-MC patients (5.3%) with no statistically significant difference. This study, also, was designed to formulate a diagnostic scoring system to differentiate MC patients from those with non-MC using clinical data and routine labs that are easily collected and implemented. In our study, independent factors associated with MC included age at the diagnosis ≥ 50 years, duration of diarrhea ≤ 6 months, PPI and/or H_2 receptors antagonist, abdominal pain, weight loss, nocturnal diarrhea, and low serum Na and/or K. Prediction of MC with high accuracy was achieved when these variables together were used in the diagnostic scoring system, with a sensitivity of 62% and specificity of 100% when a cutoff >6 was used and sensitivity of 75% and specificity of 97% by using a cutoff >5. When this scoring system is applied, the needed random colonic biopsies were precluded in 100% and 97%, respectively in non-MC patients, depending on the cutoff value used.

To maximize the sensitivity of the scoring system to predict MC patients, a cutoff value >3 would have been correctly identifying 100% of MC patients with specificity 91%, denoting that random colonic biopsies would have obviated in 91% of patients with non-MC. When this threshold was applied in the diagnostic scoring system, the total cost of random colonic biopsies and histopathological interpretation would be reduced in patients with CWND and normal colonoscopy. John and his colleagues (2015) developed a diagnostic scoring system to identify MC patients by retrospective analysis of 476 chronic diarrhea patients (85 patients were confirmed to have MC). Factors associated significantly with the presence of MC were; patient`s age ≥50 years, female gender,

PPI or NSAIDs use, abdominal pain, and weight loss. These factors assigned item scores and were used in a diagnostic scoring system. The range of this scoring system was from –8 to +38; a cutoff value ≥8 points were used to predict MC patients with 90.5% sensitivity and 45.3% specificity (AUC, 0.76) (Kane et al., 2015).

Another recent retrospective analysis of 617 patients with chronic diarrhea; of these patients 81 (13.1%) diagnosed with MC. Patients age ≥55 years, ≤6 months diarrheal duration, frequency of bowel motions ≥5 /day, body mass index (BMI) <30 kg/m^2, smoking, and current use of SSRIs/serotonin-norepinephrine reuptake inhibitors and NSAIDs were associated independently with MC. These 7 clinical variables were used in a diagnostic scoring system. Predicting MC patients with a sensitivity of 93% and specificity of 49% (AUC, 0.83) when ≥10 points were used in this scoring system. The negative predictive value (NPV) was 97.8% (95.0% to 99.1%). This scoring system had excellent sensitivity, reasonable specificity, and a high NPV to predict patients unlikely to have MC (Cotter and Pardi, 2017).

Limitations

Due to the prospective nature of the study, the sample size was the major limitation in this study.

5. CONCLUSION

In conclusion, this study showed that MC is quite not uncommon in patients with CWND and normal colonoscopy. The results confirmed that MC should be suspected in elderly patients but also can occur in younger ones. Abdominal pain, nocturnal diarrhea, and weight loss were the most common clinical predictors of MC and history of drug intake such as PPI and/or H_2-receptor antagonist and low serum Na and/or K also increase the likelihood of the presence of MC as an underlying pathology of diarrhea. Biopsy of normal colonic mucosa in a patient with CWND is emphasized to reach the definite diagnosis of MC, however, the created scoring system can identify patients with MC and lower costs by identifying unlikely MC patients who do not need biopsy evaluation.

Ethical approval for study protocol /study design /Methodology

The study was approved by the Medical Ethics Committee of Endemic medicine and Hepato-gastroenterology Department, Faculty of Medicine, Cairo university, Egypt (ethical approval code: END/1111/4/10/2016).

Informed Consent

Informed consent was obtained from all patients who participated in this study.

Conflict of interest

All authors disclose that there are no any potential conflicts (financial, professional, or personal) that are relevant to the manuscript.

Disclosure of Funding Source

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