DOI: 10.7860/JCDR/2022/52798.16445

Original Article

Pathology Section

Clinicopathological Evaluation of Chronic Diarrhoea with Microscopic Colitis: A Cross-sectional Study

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ABSTRACT

Introduction: Chronic diarrhoea is common in the older population accounting for 7-9% which often markedly affects their quality of life. The causes are many and include infectious, endocrine, metabolic, neoplastic, functional, drugs. Microscopic Colitis (MC) has emerged as a distinct diagnostic entity, where the colon appears endoscopically normal, but the biopsy reveals characteristic features in the mucosa. It has two histological forms i.e, Collagenous Colitis (CC) and Lymphocytic Colitis (LC).

Aim: To study the clinicopathological spectrum of lesions in random colonic biopsies of patients with chronic diarrhoea having normal colonoscopy.

Materials and Methods: This hospital-based cross-sectional study was conducted in Department of Pathology at JSS Hospital, Mysuru, Karnataka, India, from October 2017 to September 2019. Multiple random biopsies were taken from 80 patients with chronic diarrhoea who had normal colonoscopy. The slides were stained with Haematoxylin and Eosin (H&E) and Masson's Trichrome Stain (MTS). The histological features were studied under light microscopy and using computer-assisted image analysis. The Chi-square test was used to statistically analyse the data.

Results: The age of patients ranged from 11-82 years with a mean age of 43 years. Out of total 80 patients, 65 (81.25%) of the cases had non specific inflammation, 14 (17.4%) had microscopic colitis and 1 patient (1.25%) had probable eosinophilic colitis. The histological features were observed in computer-assisted image analysis using morphometry and interpreted by two pathologists with agreement.

Conclusion: Random biopsies are required for the diagnosis of microscopic colitis in the absence of macroscopic abnormalities on colonoscopy, which may affect the treatment strategy. A histologic examination combined with histochemical stain MTS and interpretation utilising computerised image analysis program with morphometry is more effective in cases with diagnostic uncertainty.

Keywords: Biopsy, Colonoscopy, Image analysis, Intestinal mucosa

INTRODUCTION

Chronic diarrhoea is the persistent alteration from the norm of stool consistency and increased frequency with ≥3 loose stools per day for greater than 4 week's duration [1]. Microscopic Colitis (MC) is one of the common causes of persistent diarrhoea and is divided into two subtypes i.e, Collagenous Colitis (CC) and Lymphocytic Colitis (LC). It is a triad of persistent watery non bloody diarrhoea, a normal/near normal endoscopy and distinctive tissue morphology [2-4].

When it was first described in 1980, it was thought to be a rare condition. Over the last two decades, the number of patients diagnosed with MC has shown an increasing trend [5].

The incidence and prevalence of MC in developed countries accounts for 4-13% of cases of chronic diarrhoea. In developing countries prevalence ranges from 15-50% [6]. However, physicians, especially those in primary care, are not as much aware of MC as a cause of chronic diarrhoea. It is important to create awareness among general practitioners, surgeons, and pathologists, as MC is a frequent disease and should always be considered in patients with chronic diarrhoea [7].

Though several biomarkers exist for the diagnosis of MC, there is currently no reliable marker, and Histopathological Examination (HPE) of multiple biopsies remains the cornerstone in the diagnosis of MC [5,6]. The histological identification of each lesion will help in appropriate specific treatment [6]. The histological features can be subjective. Besides the histochemical stains, the use of image analysis and morphometry may be more objective in the assessment of histological features.

Hence, objective of the present study was to use a computer-assisted image analysis tool to describe the histological features in random colonic biopsies of individuals with persistent diarrhoea who had a normal colonoscopy.

MATERIALS AND METHODS

This was a hospital-based cross-sectional study conducted in Department of Pathology at JSS, Mysuru, Karnataka, India, from October 2017 to September 2019. Institutional Ethical Committee clearance was obtained before the commencement of the study (Ethical clearance no.-JSSMC/PG/4700/2017-18).

Inclusion criteria: Biopsies of the patients who came with the history of chronic watery diarrhoea of minimum three times a day lasting for more than 4 weeks but having normal colonoscopy were included in the study.

Exclusion criteria: The patients who were passing blood and mucous in stools, known case of inflammatory bowel disease, intestinal tuberculosis, bacterial overgrowth, and visible lesions on endoscopy including ulcers, growths, and inadequate biopsy were excluded from the study. The biopsies were considered inadequate when the entire thickness of mucosa was not represented in the biopsy.

Sample size calculation: Based on the number of patients who presented with chronic diarrhoea to the Gastroenterology clinic, the sample size of 73 was calculated using the following formula [8]:

$N=Z^2pq/d^2$

where,

Z=1.96 (constant);

q=1-p;

d=margin of error;

p=proportion of prevalence

N=1.96×1.96×0.05×0.95/0.05×0.05.

Study Procedure

Patients who came to Gastroenterology Department with history of chronic diarrhoea were evaluated clinically. The clinical details such as duration of diarrhoea, other gastrointestinal symptoms such as abdominal pain, weight loss and nausea were noted. History of smoking and alcohol intake, presence of co-morbidities like hypertension, diabetes, hypothyroidism, hyperthyroidism and autoimmune diseases were documented. The laboratory data including complete blood counts, stool microscopy, thyroid, liver and renal function tests were documented, if available.

Stool microscopy: The numbers of leucocytes present were counted and expressed as the average numbers under the following categories: 0, 1-10, 11-20, 21-50 and >50 per High Power Field (HPF). The inflammation was graded arbitrarily based on the number of inflammatory cells [9] as:

- Occasional (1-4/hpf)
- Mild (5-20/hpf)
- Moderate (>20-50/hpf)
- Severe (>50/hpf)

The biopsy slides were observed for the presence of intraepithelial lymphocytes, type of inflammatory cells in lamina propria, presence of lymphoid follicles, number of eosinophils, severity of inflammation and thickness of subepithelial collagen. The severity of inflammation was categorised arbitrarily as mild when there was unequivocal increase, and severe when there was marked increase in chronic inflammatory cells [10].

Total 41 out of 80 patients underwent stool examination. Some of the patients denied, while others wanted to get it done during follow-up. Among them, some were lost for follow-up while others were free of symptoms.

All the patients were subjected to colonoscopy as a part of evaluation for chronic diarrhoea after ruling out other common causes enumerated above. Random biopsies were taken from ascending colon, descending colon, sigmoid colon, rectum and ileum from those patients who had normal colonoscopic findings. The biopsy tissue was immediately placed in separate vials with 10% formalin, processed conventionally in paraffin blocks and cut into 5 µm thick sections. The slides were stained with Haematoxylin and Eosin (H&E) and Masson's Trichrome Stain (MTS).

Criteria for the Diagnosis of Microscopic Colitis: [4,8]

Lymphocytic colitis: Mild to moderate increase in mononuclear inflammation in lamina propria, >20 Intraepithelial Lymphocytes (IEL)/100 epithelial cells, normal/slightly increased subepithelial collagen, damage to surface epithelium.

Collagenous colitis: Mild to moderate increase in mononuclear inflammation in lamina propria, subepithelial collagen >10 µ, normal/slightly increased intraepithelial lymphocytes but < than 20 IEL/100 epithelial cells, flattening and detachment of epithelial layer [4,8].

Nonspecific inflammation: This is characterised by an increase in inflammatory cells beyond what would be expected physiologically in the corresponding anatomical sites. Predominantly chronic cellular infiltrate is seen, without architectural distortion and multiple basal lymphoid aggregates or plasma cells are present immediately above the muscularis mucosae. Lack of pathological feature of other types of inflammation of colon precludes non specific type of colitis [11].

Eosinophilic colitis: This is characterised by >30 eosinophils/hpf in the lamina propria. Other histological findings are eosinophil microabscesses, eosinophilic cryptitis, and eosinophils within the surface epithelial compartment [12].

Evaluation of subepithelial collagen by morphometry on both H&E and MT stains was done in all the cases. The Olympus BX41 research microscope with Jenoptix (Germany) progress Charged-Coupled Device (CCD) camera and progress capture proimaging software was used for morphometric analysis. The digital images were captured with 1X C mount CCD adapter. After transferring the microscopic images to the computer, thickness of collagen was measured by image analysis program using free style line. Histological features were analysed in light microscopy as well as in computer assisted image analysis program by two pathologists with agreement and the findings were documented. The thickness of collagen >10 µ was considered as collagenous colitis. The Subepithelial Collagen (SEC) was measured on H&E and MTS by morphometry.

STATISTICAL ANALYSIS

It is a descriptive study and the following descriptive statistics were employed including, mean, standard deviation, frequency and percentage. Chi-square test was used to tabulate variables into categories. The statistical software namely Statistical Package for Social Sciences (SPSS) version 16.0 and Minitab (11.0) was used for the analysis of the data.

RESULTS

The age of patients ranged from 11 to 82 years, with a mean of 43±19.23 years There was a slight male preponderance with male:female ratio of 3:2. Along with chronic diarrhoea, 45 patients presented with other symptoms like pain abdomen, loss of weight and nausea which were present either alone or in combination. Total 46 patients had co-morbidities including hypertension, type 2 diabetes mellitus, hypothyroidism and ischaemic heart disease. One patient each had chronic kidney disease, schizophrenia, bronchial asthma and postrenal transplant. History of smoking and alcohol consumption was present in one case of lymphocytic colitis.

Total 65 cases revealed nonspecific inflammation of varying severity. Ileal biopsies were done in 45 cases, and majority showed mild to moderate inflammation. Out of 80, 41 patients underwent stool examination. It was mild in 14 patients (34.2%), moderate in 6 (14.6%), severe in 3 (7.3%) patients and occasional inflammatory cells in one patient.

One case of collagenous colitis showed a moderate increase in inflammatory cells. Five cases of CC showed mild increase in inflammatory cells. None of the samples revealed microorganisms. Liver Function Tests (LFT) and Renal Function Tests (RFT) were done in 46 patients as a part of evaluation, since they had co-morbidities. They were within normal limits in 43 (93%) patients. Two patients showed deranged RFT, while one patient showed deranged LFT [Table/Fig-1].

Variables	Collagenous colitis (n=10, 12.5%)	Lymphocytic colitis (n=4, 5%)	Non specific inflammation (n=65, 81.25%)	Probable eosinophilic colitis (n=1, 1.25%)
Mean age	58	52.2	50	45
Gender				
Male	6	1	33	-
Female	4	3	32	1
Symptoms				
Nausea	-	1 (1.25%)	13 (16.25%)	-
Weight loss	1 (1.25%)	-	10 (12.5%)	-
Pain abdomen	-	1 (1.25%)	18 (22.5%)	-
Alcoholic/smoker	-	1 (1.25%)	-	-
Co-morbidities				
Hypertension	2 (2.5%)	1 (1.25%)	13 (16.25%)	-
Type 2 diabetes mellitus	2 (2.5%)	1 (1.25%)	12 (15%)	-
Thyroid diseases	-	1 (1.25%)	4 (5%)	1 (1.25%)
Ischaemic heart disease	-	-	5 (6.25%)	-
Postrenal transplant	1 (1.25%)	-	-	-
Asthma	-	-	1 (1.25%)	-

Chronic kidney disease	-	-	1 (1.25%)	-
Schizophrenia	-	-	1 (1.25%)	-
Stool microscopy (n=41)				
No inflammatory cells	-	1 (1.25%)	16 (20%)	-
Occasional	-	-	1 (1.25%)	-
Mild	5 (6.25%)	-	9 (11.25%)	
Moderate	1 (1.25%)	-	5 (6.25%)	-
Severe	-	-	3 (3.75%)	-

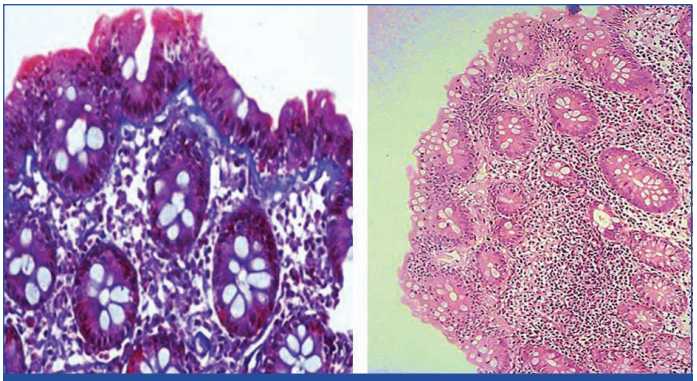
[Table/Fig-1]: Clinicopathological features in patients with chronic diarrhoea [N=80].

Histological features were observed and analysed in light microscopy. The mucosal lining epithelium was normal in 76 cases (93.8%). There was an increase in inflammatory cell infiltrate in the lamina propria in all the cases and was comprised of lymphocytes, eosinophils, plasma cells, and neutrophils in varying proportions. The other features observed were congestion and oedema, which was seen in 5 (6.25%) cases. The crypt architecture was normal in majority (n=67) of the patients. Cryptitis/crypt abscess were observed in 13 cases. Majority of the cases (47) had mild inflammation in the lamina propria, which included seven cases of collagenous colitis, two cases of lymphocytic colitis and 38 cases of non specific inflammation [Table/Fig-2]. The average normal subepithelial collagen thickness was 5.4 µ [Table/Fig-3].

Variables	Collagenous colitis (n=10, 12.5%)	Lympho-cytic colitis (n=4, 4.5%)	Non specific inflammation (n=65, 81.25%)	Probable eosinophilic colitis (n=1, 1.25%)
Mucosal lining epithelium (IELs)	Normal	Increased 4 (4.5%)	Normal	Normal
Lamina propria				
1. Number of eosinophils				
1-10	9 (11.25%)	4 (5%)	54 (67.5%)	-
11-20	1 (1.25%)	-	9 (11.25%)	-
21-30	-	-	2 (2.5%)	-
>30	-	-	-	1 (1.25%)
2. Active inflammation				
Cryptitis/crypt abscess	3 (3.75%)	1 (1.25%)	9 (11.25%)	-
3. Degree of inflammation				
Mild	7 (8.75%)	2 (2.5%)	38 (47.5%)	-
Moderate	3 (3.75%)	1 (1.25%)	27 (33.75%)	-
Severe	-	1 (1.25%)	-	1 (1.25%)
4. Lymphoid follicle				
Present	7 (8.75%)	1 (1.25%)	37 (46.25%)	-
Absent	3 (3.75%)	3 (3.75%)	29 (36.25%)	1 (1.25%)
5. Subepithelial collagen (MTS)				
1-10 µ	-	4 (5%)	65 (81.25%)	1 (1.25%)
11-20 µ	8 (10%)	-	-	-
21-30 µ	1 (1.25%)	-	-	-
>30 µ	1 (1.25%)	-	-	-
6. Congestion/ oedema			5 (6.25%)	

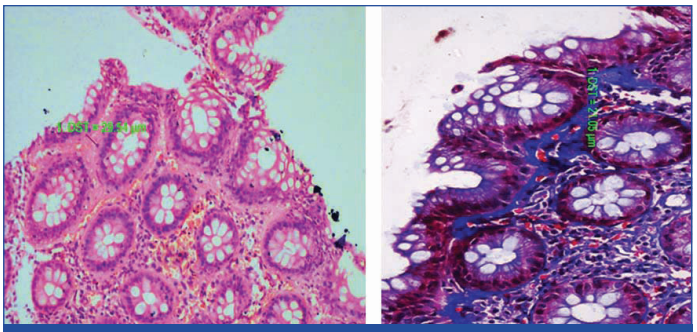
[Table/Fig-2]: Histological findings in colonic biopsies [N=80].

Active inflammation was noted in 13 (16.5%) cases. The number of eosinophils was counted per high power field in lamina propria. Scattered eosinophils were present in all the cases with 15 to 25 per hpf in eight cases. An increase in intraepithelial lymphocytes was seen in four cases and was diagnosed as lymphocytic colitis [Table/Fig-4]. The subepithelial collagen thickness was patchy to diffuse and was measured by morphometry on both H&E and MT

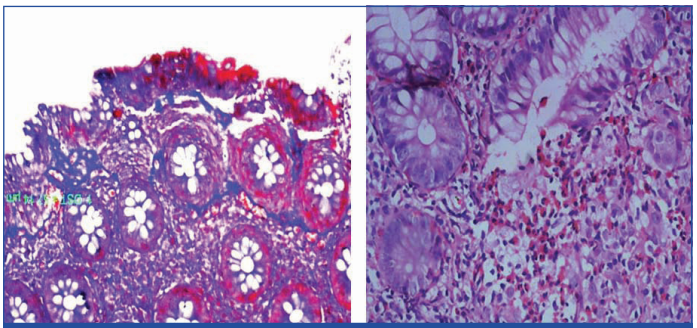


[Table/Fig-3]: Colonic biopsy with minimal nonspecific inflammation showing a thin layer of Subepithelial Collagen (SEC); (MTS, x200).
[Table/Fig-4]: Colonic biopsy showing an increase in IELs in lymphocytic colitis; (H&E, x100). (Images from left to right)

stained slides. An increase in subepithelial collagen of more than 10 µ was seen in 16 cases on H&E stain. It was confirmed by MT stain in 10 cases. The SEC thickness was in the range of 10-15 µ and more than 15 µ in five cases each which led to a diagnosis of collagenous colitis in 10 patients [Table/Fig-5-7]. The extravasated plasma and oedema in the lamina propria were falsely interpreted on H&E stain, and MT stain was used for confirmation.



[Table/Fig-5]: Collagenous colitis showing increase in Subepithelial Collagen (SEC), with moderate inflammatory infiltrate in lamina propria (H&E, x400).
[Table/Fig-6]: Collagenous colitis showing increase in SEC on MT stain (x400). (Images from left to right)



[Table/Fig-7]: Subepithelial collagen with entrapment of capillaries and detached lining epithelium; (MTS, x200). **[Table/Fig-8]:** Probable eosinophilic colitis: Colonic biopsy showing >30 eosinophils per hpf in lamina propria and intraepithelial eosinophils; (H&E, x400). (Images from left to right)

A single case showed more than 30 eosinophils per hpf and was diagnosed as probable eosinophilic colitis [Table/Fig-8]. The patient was on thyroxine for hypothyroidism and had presented with skin rashes and chronic watery diarrhoea. The patient also took Non Steroidal Anti-inflammatory Drugs (NSAID's). Her peripheral blood and bone marrow showed eosinophilia. The antinuclear antibodies, including perinuclear-antineutrophilic cytoplasmic antibodies (pANCA) and c-ANCA (cytoplasmic) were not detected. The stool microscopy did not reveal any parasites. The other laboratory parameters including LFT and RFT were within normal limits. The patient was treated with steroids and her symptoms subsided. She was on follow-up since one year with minimal dose steroids and was asymptomatic with normal blood counts. However, revised colonoscopy was not done.

DISCUSSION

The diseases associated with diarrhoea are more common in elderly population and the causes are many including infectious, endocrine, metabolic, neoplastic, functional drugs etc. [2,3]. Read and colleagues coined the term "microscopic colitis" in 1980, for patients who had chronic watery diarrhoea, with normal sigmoidoscopy and barium enema findings but with mucosal inflammation in their colonic biopsy specimens. Currently, "microscopic colitis" is a clinical term that refers to either collagenous or lymphocytic colitis [13].

In patients with normal colonoscopy, obtaining random colonic biopsies routinely to exclude microscopic colitis, is open to debate [14]. The prevalence of MC is 4-13% in developed countries, while it is high in developing countries varying from 25-50%. The high prevalence of infectious gastroenteritis in the developing countries suggests an infectious aetiology by isolation of organisms such as *Clostridium jejuni, Y. enterocolitica,* and *Clostridium difficile* in some patients and has been hypothesised, that it precipitates MC by an autoimmune reaction [13]. However, no organisms were isolated in the present study.

The mean age of patients with chronic diarrhoea was 43 years, which is in concordance with various studies [6,15]. The age ranges from 19 to 98 years and even children may be affected rarely [16]. Women are more commonly affected with Female-to-Male (F:M) ratio ranging from 3:1 to 9:1 in CC and 2.4:1 to 2.7:1 in LC [8,17]. The significance of association with gender may be undermined by the small sample size.

The patients with MC had symptoms of pain abdomen, weight loss and nausea, besides chronic watery, non bloody diarrhoea. Temmerman F and Baert F, documented pain abdomen and weight loss in many of their patients accounting to 41% and 42%, respectively [18]. The seasonal variation in symptoms is also reported [19].

The association of smoking with collagenous colitis has been reported with and without statistical significance in many studies [8,20]. Vigren L et al., in their study of 116 CC patients found 37% to be smokers. It has become apparent that smoking has a negative impact in CC and it is hypothesised, that smoking alters epigenetic events like methylation and histone modification of the genome [21]. Only one case of LC had history of smoking which was statistically not significant.

Microscopic colitis is reported to be associated with various autoimmune diseases like rheumatoid arthritis, diabetes mellitus, psoriasis, celiac disease, autoimmune thyroiditis, antiphospholipid syndrome, with presence of antinuclear antibodies [13,18,21]. Macaigne G et al., found autoimmune disease, particularly dysthyroidia to be a strong predictive factor for MC [22]. Various studies have reported thyroid disease in 8.6 to 21% MC [22,23]. In the present study, MC was associated with co-morbidities with no statistical significance.

Because of their association with a variety of autoimmune conditions, researchers have focused their attention towards investigating HLA haplotypes and serum markers in MC [13].

Autoimmune markers may be positive, including antinuclear antibodies, pANCA (antineutrophilic cytoplasmic antibodies), rheumatoid factor, and complement C3 and C4 [17]. These tests were not performed in the patients, which is a limitation. Authors found MT stain with morphometry to be very useful and objective in the interpretation of SEC thickness. The other features were moderate mononuclear inflammation in the lamina propria, flattening and detachment of epithelium. Though some authors describe the presence of IEL, others are of the opinion, that it is not required for the diagnosis of CC [3,4,8].

The consistent expression of tenascin (an extracellular matrix protein) by IHC is an excellent aid in the diagnosis of CC [18]. However, it was not done in the present study. The increased collagen is attributed to disturbances in the function of subepithelial myofibroblasts which synthesise tenascin [13]. The automated image analysis of tissue sections minimises the pathologists' interobserver variation, as emphasised by Engel PJ et al., [4].

The biopsies are recommended from cecum and transverse colon as the thickest collagen layer is observed in these anatomical regions. There was no considerable difference in the SEC thickness at different sites of colon and rectum in the present study. The computer assisted images were analysed for IEL's in LC and there was an agreement among two pathologists. The IHC for the identification of T-lymphocytes with CD3 may be done in cases of diagnostic uncertainty. Sonnenberg A et al., observed 14% of their patients with MC to have a second lymphocytic disorder of the gastrointestinal tract, and therefore any lymphocytic disorder in the lower gastrointestinal tract should raise the suspicion for a upper gastrointestinal tract related disorder and vice-versa. In the present study, the patients were anti-Tissue Transglutaminase (TTG) negative with no gluten sensitivity and hence were not subjected for upper gastrointestinal biopsy [24]. The study of rectum and sigmoid colon would provide a diagnosis in 99.5% of the patients [25].

The other histological features described in literature include, cryptitis, crypt abscesses, paneth cell metaplasia, crypt architectural distortion, surface ulceration and pseudomembranes [13]. Some of the commonly used drugs like aspirin, NSAIDS, antibiotics, ranitidine, proton pump inhibitors, β-adrenergic receptor blockers and statins are known to cause MC. There was no such association in the present study [6,13,26]. Studies from Peru and Tunis, with high prevalence of infectious gastroenteritis, revealed MC in 40% and 29.3% of cases respectively [6]. The prevalence of LC was more frequent than CC in some studies [27,28].

The patients in the present study were treated with loperamide as a first-line therapy and with budesonide for non responders. Most of the patients responded to medications. But they were lost for follow-up and hence, the data regarding management is limited. Williams JJ et al., have reported remission in 85% of LC and 91% of CC patients, when treatment is continued over six months [3].

A single case with marked mucosal eosinophilia was diagnosed as probable eosiniophilic colitis, which was attributed to NSAIDs. Eosinophilic Colitis (EC) is a rare entity and there is no consensus over its diagnosis and management. Bates AW suggests to report the mean eosinophil counts per high-power field, if it is conspicuous, and not to use the term "eosinophilic colitis" [29]. The comparison of present study with similar studies is given in [Table/Fig-9] [8,25,30,31].

Authors	Study population	Mean age (years)	Prevalence	Gender	Diagnosis			
					Lymphocytic colitis	Collagenous colitis	Probable eosinophilic colitis	Others
Yusoff IF et al., [30] (2002, Western Australia)	362	43	17.5%	F>M	0.55%	1.65	1.65%	Normal- 316; NSI-28; Melanosis coli-1
Da Silva JGN et al., [25], (2006, Brazil)	162	44.2	19.1%	F>M	11.72%	7.4%	1.23%	Crohn's-6; Melanosis coli-6; Minimal change Microscopic colitis-6
Shah RJ et al., [31] (2007, Cincinnati)	168	51	7.73%	F>M	5.95%	1.78%	0.5%	Crohn's-9; Ulcerative colitis-9; Melanosis coli-7; Infection-6
Misra V et al., [8] (2010, India)	400	52.4	3.7%	F>M	1.25%	2.5%	-	IBS-10; Infective-5
Present study, 2022 (India)	80	43	17.5%	M>F	5%	12.5%	1.25	Non specific inflammation-65

[Table/Fig-9]: Comparison of demographic and histological findings with other studies [8,25,30,31].

Limitation(s)

The CD3 T-cells, tenascin and other biomarkers were not evaluated and also the study was limited by small sample size and the lack of follow-up data in some patients.

CONCLUSION(S)

Chronic diarrhoea, is one of the common symptoms for consulting a Gastroenterologist. In the context of wide range of conditions that can result in chronic diarrhoea, a pragmatic approach is necessary in the evaluation of these patients and should include colonoscopy. In the absence of macroscopic findings on colonoscopy, random biopsies from normal appearing colon is essential for the diagnosis of microscopic colitis, which may have an impact on the treatment strategy. Histologic examination still remains a valuable tool in diagnosis of patients with suspected MC. Additional histochemical stains and interpretation using computerised image analysis program with morphometry are more objective and effective in cases with diagnostic uncertainty.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Oct 14, 2021
- Manual Googling: Mar 16, 2022
- iThenticate Software: May 19, 2022 (16%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 13, 2021**
Date of Peer Review: **Dec 14, 2021**
Date of Acceptance: **Mar 31, 2022**
Date of Publishing: **Jun 01, 2022**