THERAPEUTIC ADVANCES in
Gastroenterology

Original Research

The natural history of histological changes in microscopic colitis

Ther Adv Gastroenterol

2023, Vol. 16: 1–10

DOI: 10.1177/17562848231168237

Kanika Sehgal, June Tome, Amrit K. Kamboj, Ross A. Dierkhising, Darrell S. Pardi and Sahil Khanna

Abstract

Background: Microscopic colitis (MC) causes chronic diarrhea. It has two histologic subtypes: lymphocytic colitis (LC) and collagenous colitis (CC). Little is known about the natural progression of disease with time and with treatment.

Objectives: We aimed to assess histological changes over time.

Design: We designed a retrospective study including adults diagnosed with MC from January 1992 to January 2020 at Mayo Clinic.

Methods: Pathology reports were reviewed until 31 October 2020. Histological assessments at least 8 weeks apart were considered as adequate follow-up. Histological change from one subtype to the other and resolution were tracked with univariate and multivariable Cox proportional hazards models.

Results: Overall, 416 patients with a median age at diagnosis of 63.9 years with >1 histopathological assessment were identified. Histology at initial diagnosis was CC in 218 (52.4%) patients and LC in 198 (47.6%). No medications were associated with a histological change. However, histological resolution was more likely with the use of aspirin [hazard ratio (HR): 2.10, 95% confidence interval (CI): 1.34–3.31, $p = 0.001$) and proton-pump inhibitors (PPIs; HR: 2.01, 95% CI: 1.34–3.02, $p = 0.001$). Histological resolution was more likely with budesonide treatment (HR: 1.86, 95% CI: 1.16–3.00, $p = 0.010$) and less likely with mesalamine (HR: 0.40, 95% CI: 0.19–0.83, $p = 0.014$), compared to medications such as prednisone, loperamide, and bismuth. Patients with CC were less likely to change their histology compared to patients with LC (HR: 0.24, 95% CI: 0.14–0.42, $p < 0.001$). There was no difference in histological resolution between the two subtypes (HR: 0.70, 95% CI: 0.47–1.05, $p = 0.084$).

Conclusion: Patients with LC have a higher chance of changing their histology as compared to CC. However, histological resolution was associated with the use of PPIs and aspirin, and treatment with budesonide.

Keywords: budesonide, collagenous colitis, diarrhea, histology, lymphocytic colitis, microscopic colitis, resolution

Received: 6 November 2022; revised manuscript accepted: 21 March 2023.

Correspondence to:
Sahil Khanna
Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA
Khanna.sahil@mayo.edu

Kanika Sehgal
Department of Internal Medicine, Yale New Haven Hospital, New Haven, CT, USA

Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

June Tome
Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Amrit K. Kamboj
Darrell S. Pardi
Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Ross A. Dierkhising
Department of Quantitative Health Sciences, Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, MN, USA

Introduction

Microscopic colitis (MC) is a chronic inflammatory condition of the colon, causing watery diarrhea. Endoscopic findings are minimal or essentially normal making it a disease entity that relies on histopathology for its diagnosis.[1] Based on the histological findings, MC is subdivided into two subtypes, namely lymphocytic colitis (LC), characterized by >20 intraepithelial lymphocytes per 100 surface epithelial cells, and collagenous colitis (CC), with a thickened subepithelial collagen band (>7 μm) in addition to intraepithelial lymphocytic infiltrates.[2] Since its first description in 1985, the prevalence of MC has been increasing. Population-based studies from Olmsted County, Minnesota, showed that the incidence of MC increased from 1985 to 2001 but stabilized from 2002 to 2019 with an overall

increased prevalence in the most recent time period.[3–5]

The precise pathophysiology of MC is unknown, and treatment for the disease includes avoidance of risk factors and use of antidiarrheals or other treatments. Akin to other diseases such as celiac disease or inflammatory bowel disease, the natural histological progression of the disease is yet to be explored.[6] Understanding the histological evolution of the subtypes of MC could potentially aid in guiding the management of the disease and in determining the endpoints of treatment. This change includes changing from one MC subtype to another and resolution of histological abnormalities. In addition, the relationship between treatment and these histological changes also needs to be established.[7]

Given the paucity of data on this topic, we conducted a retrospective cohort study to determine the natural histological evolution of MC and its subtypes, along with understanding the association of treatment with these histological changes.

Methods

In this retrospective cohort study, adult patients diagnosed with MC between 1 January 1992 and 10 January 2020 at Mayo Clinic, Rochester, Minnesota, were identified using a pathology database. The diagnosis of MC was established *via* colonic biopsies reviewed by expert pathologists. Patients with index biopsies outside of Mayo Clinic, Minnesota, were also accounted for. Data were collected on patient demographics, smoking status, and medications used within 3 months of MC diagnosis such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, proton-pump inhibitors (PPIs), statins, histamine-2 antagonists, and any category of neuromodulators. Details pertaining to the diagnosis of MC at each biopsy were also collected, including date of diagnosis, MC subtype, the presence or absence of clinical symptoms, the use of medications (NSAIDs, aspirin, PPIs, statins, histamine-2 antagonists, and any category of neuromodulators) between two biopsy time points, and treatment used at each diagnosis including budesonide, prednisone, loperamide, mesalamine, bismuth, and others (mercaptopurine, sulfasalazine, azathioprine, cholestyramine, loperamide, etc.). All patients included in the study had consented to receive the treatment modalities deemed appropriate for their care. Patients with a diagnosis of inflammatory bowel disease were excluded.

In this cohort, all pathology reports from follow-up biopsies after an initial MC diagnosis were reviewed until 31 October 2020. Based on time to treatment response documented by prior clinical trials, histological assessments that were at least 8 weeks apart were considered as adequate follow-up and included.[8,9] All initial assessments that had nonspecific or mixed MC findings were not included in the analysis, and only assessments with a definitive diagnosis of either LC or CC were considered as the index diagnosis. Mixed colitis included pathological findings of CC or LC with features of another colitis.

A histological change was defined as a transition of one histological subtype to another (i.e. from LC to CC or mixed histology and from CC to LC or mixed histology). A histological resolution was defined as a transition of pathologic findings from LC or CC to normal colonic histology. Pearson's chi-squared test and analysis of variance were used to compare the LC and CC groups for baseline variables. The Kaplan–Meier method was used to estimate the median time to histological change and resolution. The Kaplan–Meier curve estimating median time does not cross 75%, making the 75th percentile undefined. Hence, the numerical estimate for the 75th percentile is reported as larger than the maximum observed follow-up time. Univariate and multivariable Cox proportional hazards models were utilized to assess predictor associations with histological change and resolution outcomes. Multivariable analysis was carried out by controlling for age, gender, smoking status, presence of clinical symptoms, the use of implicated medications, treatments, and initial histology. The statistical software R version 3.6.2 was used for statistical analysis.[10] The reporting of this study conforms to the STROBE statement.[11]

Results

Baseline characteristics

A total of 416 patients with a diagnosis of MC (either LC or CC) and >1 histopathological assessment were included (Table 1). The median age at MC diagnosis was 65 years [interquartile range (IQR): 52.4–71.7) and patients with LC

Table 1. Patient characteristics represented as *N* (%).[1]

Characteristics	LC (*N* = 198)	CC (*N* = 218)	Total (*N* = 416)	*p* Value
Sex				0.052
Female	146 (73.7%)	178 (81.7%)	324 (77.9%)	
Male	52 (26.3%)	40 (18.3%)	92 (22.1%)	
Age at diagnosis				0.033
Median (Q1, Q3)	63.9 (49.2, 70.8)	66.3 (55.6, 72.9)	65 (52.4, 71.7)	
Symptoms at initial diagnosis				0.42
N-Missing	1	8	9	
No	5 (2.5%)	3 (1.4%)	8 (2.4%)	
Yes	192 (97.5%)	207 (98.6%)	399 (98%)	

[1]Index biopsies with mixed MC findings were not included in the analysis, and only assessments with a definitive diagnosis of CC or LC were considered as the index diagnosis.
CC, collagenous colitis; LC, lymphocytic colitis; MC, microscopic colitis; Q1, quartile 1; Q3, quartile 3.

were younger [median 64 years (IQR: 49.2–70.8)] than CC [median 66.3 years (IQR 55.6–72.9), $p = 0.033$]. Overall, 324 (77.9%) patients were female, with no differences in female distribution between LC (73.7%) and CC (81.7%) ($p = 0.052$). CC ($n = 218$, 52.4%) was more common at initial MC diagnosis compared to LC ($n = 198$, 47.6%) (Table 1). Median follow-up time was similar for LC and CC [median 4.1 years (IQR: 1.7–7.7 years) for LC and median 4.5 years (IQR: 2.4–7.8 years) for CC]. No patient had a co-diagnosis of celiac disease. We had 14 patients who previously had inflammatory bowel disease, prior to our study and subsequently developed into a subtype of MC during our study time frame. During this time, they had no histological or clinical evidence of inflammatory bowel disease and were included.

Associations with histological change

On second histological assessment, there were fewer patients with CC ($n = 22/218$, 10.1%) that converted to LC compared to those with LC ($n = 51/198$, 25.7%) that converted to CC on follow-up. An additional four (2.0%) patients with LC and one (0.4%) patient with CC converted to a mixed subtype.

Overall, among the 198 patients with LC, 66 (33.3%) had a histological change during follow-up with a median time of 9.3 years (IQR: 5.3–12.9 years, $p < 0.001$). In the 226 CC patients, 25 (11.5%) had a histological change with a median time NA (IQR: 13.9–NA years, $p < 0.001$). Univariate Cox models (Table 2(a)) showed that prednisone [hazard ratio (HR): 2.6, 95% CI: 1.25–5.45, $p = 0.011$] or bismuth subsalicylate (HR: 1.68, 95% CI: 1.11–2.54, $p = 0.014$) use was associated with a higher chance of histological change. Patients with CC were not as likely to change their histology as compared to patients with LC (HR: 0.27, 95% CI: 0.17–0.43, $p < 0.001$).

A multivariable analysis (Table 2(b)) for change controlling for age, gender, smoking status, presence of clinical symptoms, the use of implicated medications, treatment, and initial histology revealed that treatment with prednisone (HR: 2.47, 95% CI: 0.94–6.53, $p = 0.067$) or bismuth subsalicylate (HR: 1.34, 95% CI: 0.82–2.18, $p = 0.24$) was not associated with a histological change. On multivariate analysis, patients with CC were not as likely to change their histology as compared to patients with LC (HR: 0.24, 95% CI: 0.14–0.42, $p < 0.001$).

Associations with histological resolution

On only the second histological assessment, histology normalized in fewer CC patients ($n = 38/218$, 17.4%) compared to LC patients ($n = 54/198$, 27.3%).

Table 2(a). Univariate Cox model for outcome of histological change (i.e. from LC to CC or mixed histology and from CC to LC or mixed histology).[a]

Term	HR	HR 95% lower	HR 95% upper	*p* Value
Former smoking *versus* never smoker	1.078	0.673	1.728	0.754
Current smoking *versus* never smoker	0.855	0.482	1.515	0.591
Age at diagnosis	1.008	0.992	1.025	0.334
Male *versus* female	1.024	0.622	1.685	0.926
NSAID use	1.058	0.616	1.817	0.837
Aspirin use	0.867	0.521	1.442	0.582
PPI use	1.042	0.631	1.721	0.871
Statin use	0.809	0.460	1.421	0.460
Histamine-2 antagonist use	0.343	0.048	2.474	0.289
Antipsychotic medication use	1.186	0.730	1.928	0.490
Budesonide treatment	1.205	0.749	1.940	0.442
Prednisone treatment	2.609	1.249	5.451	0.011
Imodium treatment	1.260	0.832	1.908	0.274
Mesalamine treatment	0.835	0.472	1.478	0.536
Bismuth treatment	1.680	1.109	2.545	0.014
Other treatment options	0.684	0.371	1.261	0.224
Presence of symptoms	2.990	0.731	12.231	0.127
CC *versus* LC	0.270	0.170	0.430	<0.001

[a]Index biopsies with mixed MC findings were not included in the analysis, and only assessments with a definitive diagnosis of CC or LC were considered as the index diagnosis. Mixed MC findings were only included if found after an index biopsy. CC, collagenous colitis; HR, hazard ratio; LC, lymphocytic colitis; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor.

Overall, in the 198 patients with LC, 62 (31.3%) had histological resolution during follow-up with a median resolution time of 9.6 years (IQR: 5.0–NA years). In the 218 patients with CC, 54 (24.8%) had a histological resolution with a median resolution time of 13.5 years (IQR: 6.4–NA years). Univariate Cox models for resolution (Table 3(a)) showed that the use of aspirin and PPI was associated with a resolution of histology (HR: 1.62, 95% CI: 1.10–2.4, $p=0.015$ and HR: 2.28, 95% CI: 1.55–3.36, $p<0.001$, respectively). Treatment with budesonide was associated with resolution (HR 2.00, 95% CI: 1.38–2.92, $p<0.001$), while treatment with mesalamine was less likely to be associated with histological resolution (HR: 0.40, 95% CI: 0.20–0.79, $p=0.008$). CC had a similar chance of resolution as compared to LC (HR: 0.74, 95% CI: 0.51–1.06, $p=0.10$).

On multivariable analysis for resolution controlling for age, gender, smoking status, the presence of clinical symptoms, the use of implicated medications, treatment, and initial histology (Table 3(b)), the use of aspirin (HR: 2.10, 95% CI: 1.34–3.31, $p=0.001$) or PPI (HR: 2.01, 95% CI: 1.34–3.02, $p=0.001$) was associated with histological resolution. Treatment with budesonide had a higher chance of resolution (HR: 1.86, 95% CI: 1.16–3.00, $p=0.010$), while

Table 2(b). Multivariable Cox model for outcome of histological change (i.e. from LC to CC or mixed histology and from CC to LC or mixed histology).[a]

Term	HR	HR 95% lower	HR 95% upper	*p* Value
Former smoking *versus* never smoker	0.970	0.573	1.642	0.910
Current smoking *versus* never smoker	0.836	0.397	1.761	0.638
Age at diagnosis	1.015	0.994	1.037	0.158
Male *versus* female	1.099	0.606	1.995	0.755
NSAID use	1.051	0.598	1.847	0.864
Aspirin use	0.764	0.430	1.358	0.358
PPI use	1.161	0.675	1.997	0.590
Statin use	0.609	0.329	1.127	0.114
Histamine-2 antagonist use	0.534	0.071	3.999	0.541
Antipsychotic medication use	0.846	0.471	1.517	0.574
Budesonide treatment	1.398	0.744	2.607	0.300
Prednisone treatment	2.475	0.938	6.527	0.067
Imodium treatment	1.295	0.720	2.321	0.388
Mesalamine treatment	0.930	0.474	1.826	0.833
Bismuth treatment	1.339	0.822	2.183	0.241
Other treatment options	0.986	0.461	2.110	0.971
Presence of symptoms	2.283	0.501	10.396	0.286
CC *versus* LC	0.245	0.141	0.426	<0.001

[a]Index biopsies with mixed MC findings were not included in the analysis, and only assessments with a definitive diagnosis of CC or LC were considered as the index diagnosis. Mixed MC findings were only included if found after an index biopsy. CC, collagenous colitis; HR, hazard ratio; LC, lymphocytic colitis; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor.

treatment with mesalamine did not (HR: 0.40, 95% CI: 0.19–0.83, $p=0.014$). Furthermore, CC had a similar chance of resolution as compared to LC (HR: 0.70, 95% CI: 0.47–1.05, $p=0.08$).

Discussion

In this study, we found that treatment with budesonide was associated with histological resolution in patients with MC. We found that changing of histological subtypes was not associated with the use of any medication. Patients with LC are more likely to change their histology as compared to patients with CC. Histological resolution was associated with use of aspirin and PPIs, and with treatment with budesonide, while mesalamine treatment was less effective. There were no differences between patients with LC and CC in histological resolution.

The natural course of changes in histology in MC patients relative to the specific treatment used has not been studies previously. A small study with 31 patients was conducted to understand the relationship between symptoms and histological changes in MC and found no association between treatment and change in symptoms or histological findings.[6] Another study aimed to understand the temporal evolution of histological changes of MC pre- and post-diagnosis and demonstrated that

Table 3(a). Univariate Cox model for outcome of resolution (from LC or CC to normal colonic histology).[a]

Term	HR	HR 95% lower	HR 95% upper	*p* Value
Former smoking *versus* never smoker	0.901	0.582	1.396	0.641
Current smoking *versus* never smoker	1.161	0.734	1.837	0.524
Age at diagnosis	0.999	0.986	1.013	0.924
Male *versus* female	0.809	0.509	1.287	0.371
NSAID use	0.951	0.600	1.510	0.833
Aspirin use	1.624	1.100	2.399	0.015
PPI use	2.286	1.557	3.356	<0.001
Statin use	1.062	0.678	1.664	0.794
Histamine-2 antagonist use	0.503	0.124	2.039	0.336
Antipsychotic medication use	1.314	0.869	1.988	0.196
Budesonide treatment	2.009	1.381	2.923	<0.001
Prednisone treatment	1.441	0.668	3.109	0.352
Imodium treatment	0.812	0.558	1.180	0.274
Mesalamine treatment	0.397	0.201	0.786	0.008
Bismuth treatment	0.822	0.552	1.226	0.337
Other treatment options	0.893	0.539	1.479	0.661
Presence of symptoms	0.737	0.341	1.591	0.437
CC *versus* LC	0.736	0.511	1.061	0.100

[a]Index biopsies with mixed MC findings were not included in the analysis, and only assessments with a definitive diagnosis of CC or LC were considered as the index diagnosis. Mixed MC findings were only included if found after an index biopsy.
CC, collagenous colitis; HR, hazard ratio; LC, lymphocytic colitis; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor.

histology in MC normalized in a minority of patients with recurrence or persistent diarrhea.[7]

Current guidelines implicate PPIs as a risk factor for MC.[12,13] A few studies have found a negative association between PPIs and MC, whereas other studies found no association when patients with MC were compared to both controls chosen randomly and those with diarrhea.[14] However, this study was limited by a smaller sample size. A recent, larger multi-center retrospective cohort study included patients with biopsy-proven MC as cases and patients who underwent colonoscopy for the evaluation of diarrhea with biopsies negative for MC as controls.[15] They found an inverse relation between the use of PPIs and the presence of MC. Our results suggest a similar relationship between PPIs and MC, where PPIs seemed to be linked with histological resolution in patients with MC.

Data on the association of aspirin with MC are limited. One population-based case–control study aimed to evaluate the risk of MC with the use of drugs such as low-dose aspirin.[16] In this study, the use of low-dose aspirin was associated with an increased risk of MC (odds ratio: 17.6, 95% CI: 1.9–165.9). However, another prospective comparative study assessed the colonic histology for MC features in asymptomatic chronic low-dose aspirin users and non-users undergoing primary screening colonoscopy.[17] Of the 100 subjects

Table 3(b). Multivariable Cox model for outcome of resolution (from LC or CC to normal colonic histology).[a]

Term	HR	HR 95% lower	HR 95% upper	*p* Value
Former smoking *versus* never smoker	0.862	0.532	1.397	0.546
Current smoking *versus* never smoker	1.140	0.677	1.918	0.623
Age at diagnosis	0.999	0.980	1.017	0.879
Male *versus* female	0.873	0.520	1.466	0.607
NSAID use	1.091	0.676	1.759	0.722
Aspirin use	2.104	1.337	3.311	0.001
PPI use	2.012	1.340	3.023	0.001
Statin use	1.022	0.626	1.668	0.931
Histamine-2 antagonist use	0.470	0.111	1.995	0.306
Antipsychotic medication use	1.215	0.774	1.907	0.397
Budesonide treatment	1.856	1.157	2.977	0.010
Prednisone treatment	1.445	0.631	3.311	0.384
Imodium treatment	0.842	0.526	1.347	0.473
Mesalamine treatment	0.398	0.191	0.829	0.014
Bismuth treatment	1.025	0.657	1.599	0.913
Other treatment options	1.270	0.673	2.399	0.461
Presence of symptoms	0.717	0.289	1.777	0.473
CC *versus* LC	0.701	0.468	1.049	0.084

[a]Index biopsies with mixed MC findings were not included in the analysis, and only assessments with a definitive diagnosis of CC or LC were considered as the index diagnosis. Mixed MC findings were only included if found after an index biopsy.
CC, collagenous colitis; HR, hazard ratio; LC, lymphocytic colitis; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor.

included in the study, 42 were recognized as aspirin users. They observed no features of MC on histology and found no relationship between aspirin and development of MC. Our findings are similar to these results, where the use of aspirin does not seem to be implicated in the direct causation of MC.

Various clinical trials have shown budesonide to be effective for clinical remission in MC.[9,18–20] The American Gastroenterology Association guideline on the medical management of MC states budesonide as the first-line treatment option in MC to achieve clinical remission.[12] Similarly, the guidelines from the United European Gastroenterology and European Microscopic Colitis Group recommend the use of budesonide to induce and maintain remission in patients with MC as well.[12] Our study contributes to the current data on the clinical efficacy of budesonide by also providing evidence of histological resolution with budesonide. It is possible that higher chances of histological remission with budesonide could contribute to its clinical benefit. While clinical remission is considered to be the endpoint for MC therapy, histological remission could serve as a potential endpoint for patients with refractory MC. It appears that budesonide decreases inflammation in MC, which thereby results in complete resolution.

A clinical trial found that mesalamine was an effective therapeutic option for LC and when used in combination with cholestyramine, it was more useful for treatment of CC.[21] In contrast, other clinical trials have not shown efficacy of mesalamine over budesonide or placebo.[18,22] Guidelines from the United European Gastroenterology and European Microscopic Colitis Group recommend against the use of mesalamine for the treatment of MC.[12] However, guidelines from the American Gastroenterological Association suggest the use of mesalamine for MC in patients that do not respond to budesonide therapy.[12] While mesalamine administration might be useful for mitigation of diarrheal symptoms in patients with MC, our findings indicate that mesalamine does not result in histological resolution. This could imply that mesalamine might not be useful for the management of refractory MC, where the disease might still be histologically persistent.

Our study had several limitations. First, the nature of the study was retrospective leading to small amount of missing data such as length of treatment. Second, being retrospective, colonic biopsies were not performed and assessed at uniform intervals. Third, the dose and length of treatment with budesonide administered at each biopsy was not accounted for. However, a recent study from Mayo Clinic reported the clinical efficacy of budesonide for MC treatment at a dose as low as 3 mg per day or every other day, and also reported safety with long-term use.[23] Lastly, the exact dosage and length of medications potentially implicated as risk factors could not be accounted for. Medications reported at one biopsy and at the successive biopsy were used continuously within that time frame. While medications reported at the first biopsy but not the successive biopsy were discontinued within that time frame. This limits us from assessing the adequate dosage and length of use of medications that could impact histological change or resolution.

Given the similar resolution rates of LC and CC, it is likely that management does not need to be tailored based on subtypes of MC and treatment options remain the same for both. The initial step to treat MC entails avoiding medications, such as PPIs and aspirin, which could be implicated in the causation of the disease.[2] However, the relationship between the use of PPIs and aspirin with histological resolution suggested by our study could imply that these medications do not directly cause MC. Since it is unclear whether histological remission is necessary for MC,[24] symptom resolution remains the endpoint of treatment. In light of our findings, future studies should assess whether using histological resolution is an important endpoint when treating with budesonide, if for example that would decrease the risk of recurrent diarrhea after discontinuation of budesonide.

In conclusion, this is the first study investigating the association of medications and treatment with histological evolution of both MC subtypes. We found that change in histological subtypes of MC was independent of medications used. In addition, the use of PPIs and aspirin was associated with a greater chance of histological remission in MC patients. We also found that treatment with budesonide was associated with a higher chance of resolving MC histology. However, treatment with mesalamine was not significantly effective with regards to MC histology. Furthermore, patients with LC have a higher chance of changing their histological findings as compared to patients with CC. Larger, prospective studies are needed to further affirm the relationship between PPI and aspirin usage and budesonide treatment with changes in histology of MC patients. Also, future studies should evaluate histological endpoints with treatment in patients with MC.

Previous presentations

These data were presented at the Digestive Diseases Week 2021 online meeting as a poster of distinction.

Declarations

Ethics approval and consent to participate

Ethical approval has been granted by the IRB. IRB ID – 16-006819. Only patients who have consented to participate in research were included.

Consent for publication

No patient images were used in this study. Only patients who consented to have their information used for research were included in the study.

Author contributions

Kanika Sehgal: Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

June Tome: Data curation; Writing – review & editing.

Amrit K. Kamboj: Writing – review & editing.

Ross A. Dierkhising: Formal analysis; Writing – review & editing.

Darrell S. Pardi: Conceptualization; Supervision; Writing – review & editing.

Sahil Khanna: Conceptualization; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Acknowledgements
None.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by a small grants project award from the division of Gastroenterology and Hepatology at Mayo Clinic, Rochester, MN.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

ORCID iDs
Kanika Sehgal https://orcid.org/0000-0002-0186-3583
Sahil Khanna https://orcid.org/0000-0002-7619-8338

Supplemental material
Supplemental material for this article is available online.

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