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Case Series

Biopsy-Detected Microscopic Colitis and Nonspecific Chronic Inflammatory Change in Patients with Chronic Diarrhea and Normal Colonoscopy: A Two-Case Series

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ABSTRACT

Chronic diarrhea may occasionally persist despite macroscopically normal colonoscopy, and in selected patients, random colonic biopsy may reveal histologic abnormalities not apparent endoscopically. We report two illustrative cases of biopsy-detected microscopic or nonspecific inflammatory abnormalities in patients initially managed as having a functional bowel disorder. This retrospective descriptive case series included two adults identified during routine clinical practice over a recent two-year period (approximately 2024–2025) at a tertiary care hospital who underwent colonoscopy with random colonic biopsies despite macroscopically normal colonic mucosa, due to persistent diarrhea-predominant symptoms. Clinical follow-up was available for approximately six weeks in Case 1 and eight weeks in Case 2. In both patients, colonoscopy revealed macroscopically normal colonic mucosa, except for hemorrhoids. In Case 1, histopathology showed preserved crypt architecture, increased intraepithelial lymphocytes, and mild lamina propria inflammation, consistent with lymphocytic microscopic colitis. In Case 2, biopsy showed increased intraepithelial lymphocytes with chronic inflammatory infiltrates in the lamina propria, interpreted as nonspecific chronic inflammatory change. Both patients received colonic-release budesonide with short-term subjective symptomatic improvement on available follow-up. These cases illustrate that biopsy-detected microscopic or nonspecific inflammatory abnormalities may occasionally be identified in selected patients with persistent diarrhea and normal colonoscopy. They should not be interpreted as evidence of routine biopsy yield, but they support individualized biopsy decisions in carefully selected patients after exclusion of more common causes.

1. Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by recurrent abdominal symptoms associated with altered bowel habits in the absence of structural disease [1, 2]. In routine practice, however, patients initially labeled as having “IBS-like” symptoms may later prove to have an organic disorder, particularly when diarrhea-predominant symptoms persist despite empirical therapy [2, 3].

Microscopic colitis is a recognized cause of chronic watery diarrhea that often presents with normal or near-normal colonoscopic findings and requires histopathological confirmation [4, 5]. In contrast, nonspecific chronic inflammatory changes on random colonic biopsy are less diagnostically specific. They may reflect a range of processes, including post-infectious change, medication-related injury, resolving inflammation, or early/indeterminate inflammatory conditions. These entities should therefore not be interpreted as equivalent.

Current clinical practice supports selective rather than routine random colonic biopsy in patients with chronic watery diarrhea and normal endoscopy, particularly when symptoms are persistent, unexplained after basic evaluation, or refractory to standard therapy [6–9]. We present two illustrative cases in which a random colonic biopsy performed in the setting of persistent diarrhea and macroscopically normal colonoscopy demonstrated biopsy-based abnormalities that altered subsequent management.

2. Methods

This report is a retrospective descriptive case series of two adult patients evaluated in routine clinical practice at a tertiary care hospital. Cases were identified from endoscopy and pathology records over a recent two-year period (approximately January 2024 to December 2025) in which patients underwent colonoscopy with random colonic biopsies despite macroscopically normal colonic mucosa due to persistent diarrhea-predominant symptoms.

This manuscript is intended as an illustrative case series rather than an estimate of diagnostic yield. No denominator analysis was performed, and the report does not quantify the frequency with which random biopsies were negative during the study period.

Clinical data were obtained from chart review, including symptom duration, prior working diagnosis, colonoscopic findings,

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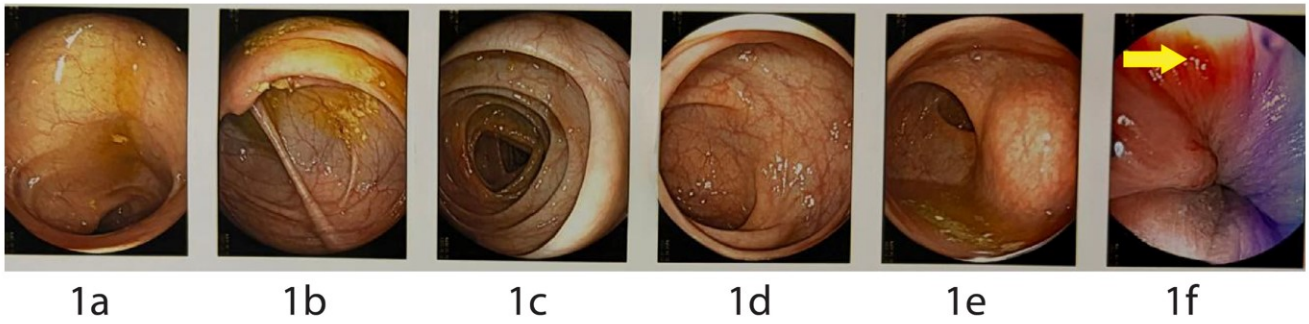


Figure 1: Colonoscopic images from Case 1 showing macroscopically normal colonic mucosa with hemorrhoids in the anal canal (yellow arrows).

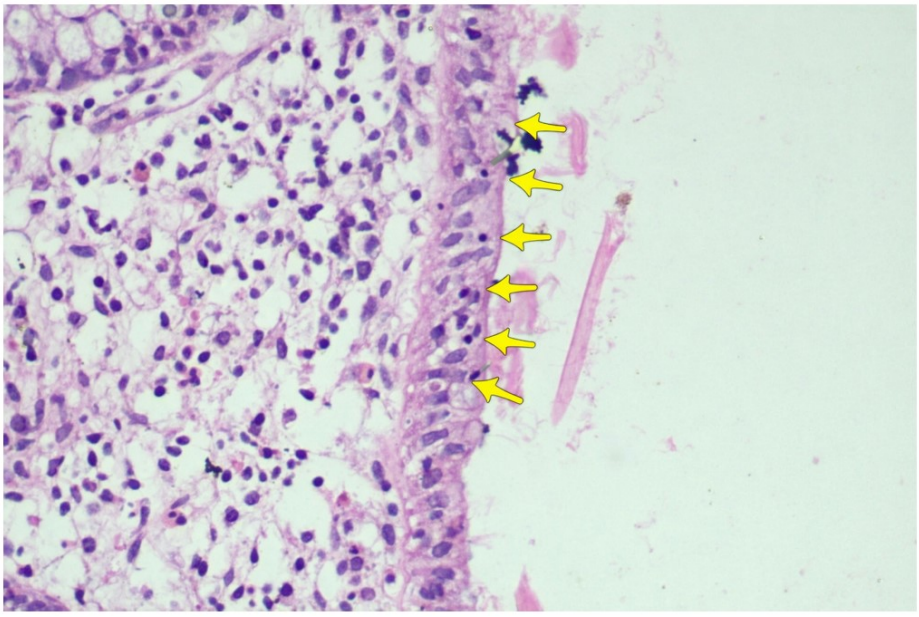


Figure 2: Histopathological section of colonic biopsy from Case 1 showing increased intraepithelial lymphocytes (yellow arrows) and mild lamina propria inflammation, consistent with lymphocytic microscopic colitis (H&E stain).

histopathology, treatment, and available follow-up. Written informed consent for publication of anonymized clinical details and images was obtained from both patients. This case series reflects routine clinical care and was not designed as an interventional study.

Random biopsies were obtained from macroscopically normal-appearing colonic mucosa at the treating gastroenterologist's discretion because of persistent symptoms despite prior symptomatic management. In both cases, biopsy samples were documented as having been taken from endoscopically normal colonic mucosa; however, the exact segmental distribution (including right-versus-left colonic sampling) and the exact number of biopsies were not consistently available in the archived procedural records. Accordingly, this report should not be interpreted as reflecting a standardized or reproducible biopsy protocol. Histopathological interpretation was based on routine pathology reporting. In Case 1, the biopsy findings were considered consistent with lymphocytic microscopic colitis. In Case 2, the findings were interpreted more cautiously as nonspecific chronic inflammatory change rather than a definitive, discrete inflammatory colitis syndrome.

Alternative causes of chronic diarrhea were assessed clinically before colonoscopy, including symptom review, medication history, routine laboratory evaluation, and endoscopic exclusion of gross structural pathology. However, the retrospective nature of this report limits the completeness of uniform documentation for stool testing, celiac serology, and other secondary-cause exclusion across both cases, and this is acknowledged as a limitation.

3. Case Series

3.1. Case 1

A 43-year-old woman presented with a six-month history of chronic loose stools with increased stool frequency and intermittent abdominal discomfort. She had previously been managed symptomatically for a functional bowel disorder without sustained improvement. There was no history of gastrointestinal bleeding, clinically significant weight loss, nocturnal diarrhea, or family history of inflammatory bowel disease. The available chart review documented basic laboratory assessment, including routine hemogram and biochemical evaluation, without evidence of overt systemic inflammatory or metabolic disease. Medication review did not identify a clearly

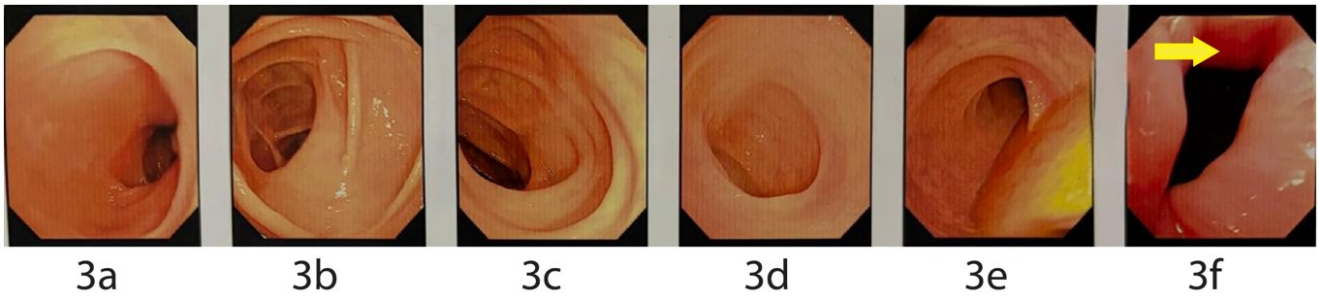


Figure 3: Colonoscopic images from Case 2 demonstrating macroscopically normal colonic mucosa with hemorrhoids in the anal canal (yellow arrows).

documented precipitating drug exposure. Stool studies and celiac serology were not uniformly documented in the retrospective record; therefore, complete standardized exclusion of all secondary causes cannot be confirmed.

Because of persistent diarrhea-predominant symptoms despite prior empirical treatment, colonoscopy was performed. This demonstrated hemorrhoids with otherwise macroscopically normal colonic mucosa **(Figure 1)**. Random biopsies were obtained from normal-appearing colonic mucosa, but the exact segmental biopsy distribution and number of fragments were not consistently available in the archived endoscopy record.

Histopathological examination showed preserved crypt architecture with a focal increase in intraepithelial lymphocytes and mild lamina propria inflammation **(Figure 2)**. In the clinical and histologic context, this was interpreted as consistent with lymphocytic microscopic colitis [4, 5]. The patient was treated with colonic-release budesonide. Available follow-up documentation reflected short-term symptomatic improvement over approximately six weeks. Longer-term relapse status after tapering was not uniformly available in the archived record. No repeat histology or objective inflammatory biomarker reassessment was performed.

3.2. Case 2

A 37-year-old man presented with approximately 1.5 years of chronic loose stools associated with bloating. He had previously been labeled as having IBS and treated symptomatically without meaningful improvement. There was no history of overt gastrointestinal bleeding, major weight loss, or nocturnal symptoms documented in the available records. The available chart review documented a basic laboratory assessment without clear abnormality, and the medication review did not identify a clearly documented high-risk exposure. However, stool studies, celiac serology, and complete standardized secondary-cause evaluation were not uniformly documented in the retrospective record and, therefore, cannot be considered comprehensively excluded.

Because of persistent diarrhea despite prior symptomatic therapy, a colonoscopy was performed. The colonic mucosa appeared macroscopically normal except for hemorrhoids **(Figure 3)**. Random colonic biopsies were obtained from normal-appearing mucosa, but exact segmental biopsy distribution and biopsy counts were not uniformly available in the archived record.

Histopathology demonstrated increased intraepithelial lymphocytes with chronic inflammatory infiltrates in the lamina propria **(Figure 4)**. Unlike Case 1, these findings were considered less specific and were interpreted more cautiously as nonspecific chronic inflammatory change rather than a definitive microscopic colitis subtype. Given the persistent symptoms, absence of gross endoscopic disease, and biopsy-based inflammatory changes, a therapeutic trial of colonic-release budesonide was undertaken after clinical correlation. The available follow-up documentation reflected short-term subjective improvement over approximately eight weeks after initiation of budesonide. However, the retrospective record did not clearly document a complete tapering schedule, longer-term relapse status, or repeat objective reassessment. Therefore, longer-term diagnostic stability for Case 2 remains uncertain.

4. Discussion

This report describes two illustrative cases in which random colonic biopsy obtained during macroscopically normal colonoscopy demonstrated histologic abnormalities in patients with persistent diarrhea-predominant symptoms initially managed as functional bowel disorder. Importantly, this case series should not be interpreted as evidence of diagnostic yield or broad “diagnostic utility,” because only two positive cases are presented, and no denominator is provided for the number of patients with normal colonoscopy who underwent biopsy during the same period.

The first case is the more diagnostically robust of the two. The histologic finding of increased intraepithelial lymphocytes with preserved crypt architecture and mild lamina propria inflammation is compatible with lymphocytic microscopic colitis in the appropriate clinical setting [4, 5]. Microscopic colitis is a well-recognized cause of chronic watery diarrhea with normal or near-normal endoscopic appearance, and selective biopsy is appropriate when diarrhea is persistent, unexplained, and disproportionate to a purely functional diagnosis [6–9].

The second case requires greater caution. The label of nonspecific chronic inflammatory change does not by itself establish a discrete inflammatory colitis syndrome. Such changes may be seen in a range of contexts, including post-infectious change, medication-related injury, early or indeterminate inflammatory disease, or nonspecific reactive inflammation. Accordingly, this case should be viewed as an example of biopsy-detected nonspecific inflammatory abnormality rather than definitive proof of a well-defined inflammatory colitis entity.

The short-term symptomatic improvement observed after budesonide in both patients should also be interpreted cautiously. A therapeutic response, especially in a patient with less specific histology, should not be regarded as diagnostic confirmation. In the second case in particular, budesonide was used as a clinically reasoned therapeutic trial in the setting of persistent symptoms and biopsy-based inflammatory change. Still, the response does not establish etiologic certainty.

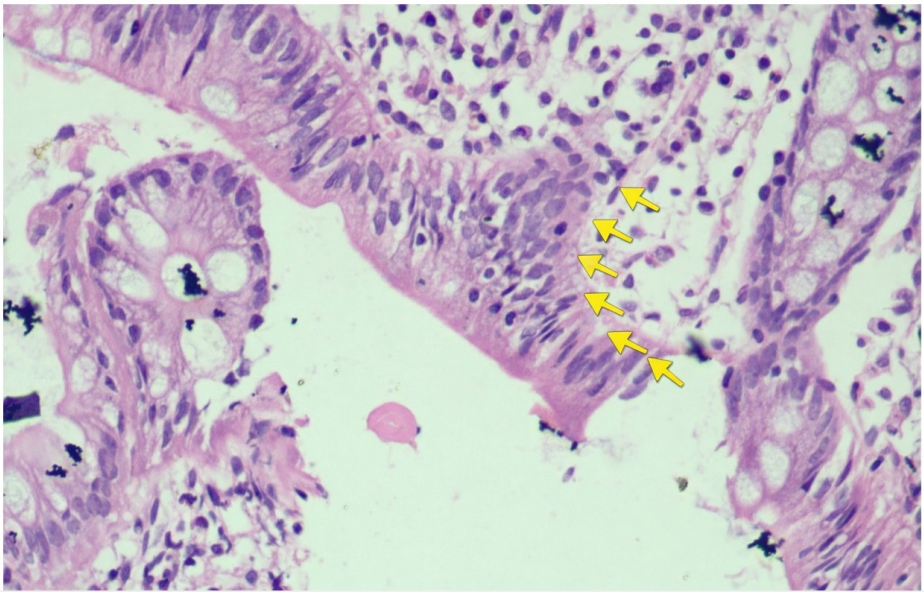


Figure 4: Hematoxylin and eosin-stained colonic biopsy from Case 2 showing increased intraepithelial lymphocytes (yellow arrows) and chronic inflammatory infiltrates within the lamina propria, interpreted more cautiously as nonspecific chronic inflammatory change rather than a definitive microscopic colitis subtype. (Original pathology report basis; exact magnification not available from archived image.)

Recent guideline-based literature supports a selective rather than indiscriminate biopsy approach in patients with chronic watery diarrhea and normal endoscopy, particularly when symptoms are persistent, unexplained, or clinically discordant with a straightforward functional diagnosis [6–9]. Contemporary guidance emphasizes histologic confirmation for microscopic colitis while recognizing that diagnostic yield is influenced by pretest probability and biopsy adequacy [6].

Both patients in this series represented comparatively low-pretest-probability presentations for biopsy-detected microscopic or inflammatory abnormalities because they were younger than the typical demographic in whom microscopic colitis is classically emphasized and lacked strongly suggestive alarm features. This lower pretest probability is important when interpreting the manuscript, because it limits generalizability and reinforces that biopsy in these cases reflected individualized clinical judgment in the setting of persistent, treatment-refractory diarrhea rather than a broadly applicable rule.

These cases support a selective, individualized approach rather than routine random biopsy in all patients with IBS-like symptoms. Biopsy is more defensible in patients with persistent diarrhea-predominant symptoms, chronic watery stools, failure of standard symptomatic therapy, or clinical concern that exceeds the pretest probability of a purely functional disorder. Conversely, indiscriminate biopsy in all patients with a normal colonoscopy may increase costs, yield nonspecific histologic findings, and risk over-interpretation without necessarily improving management.

5. Limitations

This report has several important limitations. First, it is a two-patient retrospective case series and is inherently hypothesis-generating rather than practice-defining. Second, no sampling denominator is provided, so the biopsy yield cannot be estimated. Third, the workup for secondary causes of chronic diarrhea was not uniformly documented in a protocolized manner across both patients because of retrospective data capture. Fourth, biopsy protocol details, including exact segmental sampling and standardized histologic thresholds, were not completely available in the chart for both cases. Fifth, pathology was interpreted in routine clinical practice, and the manuscript does not include formal blinded re-review by a gastrointestinal pathologist. Finally, clinical improvement was assessed by short-term subjective symptom follow-up rather than standardized outcome metrics, biomarker reassessment, or long-term relapse documentation.

Overall, the present report is best understood as a small illustrative case series demonstrating that biopsy-detected microscopic or nonspecific inflammatory abnormalities may occasionally be encountered in selected patients with persistent diarrhea and normal colonoscopy. It should not be used to justify routine biopsy in all patients with generic IBS-like presentations.

6. Conclusion

This two-case series illustrates that biopsy-detected microscopic or nonspecific inflammatory abnormalities may occasionally be identified in carefully selected patients with persistent diarrhea-predominant symptoms despite macroscopically normal colonoscopy. These observations should not be interpreted as evidence of routine diagnostic yield or broad practice-changing utility. Rather, they support a selective, individualized decision to obtain random colonic biopsies in patients whose clinical presentation remains atypical for uncomplicated functional bowel disorder after appropriate evaluation.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Informed Consent

Written informed consent for publication of anonymized clinical details and images was obtained from both patients.

Large Language Model

The authors used ChatGPT (OpenAI: GPT-5 series) for language editing, grammar refinement, and formatting assistance during manuscript preparation. The authors independently reviewed, verified, and approved all scientific content and take full responsibility for the accuracy and integrity of the manuscript.

Author Contributions

JT handled conceptualization, data curation, investigation, literature review, drafting the manuscript, review and editing, and coordination of the submission. NA supervised the work, managed the patient, performed the endoscopic evaluation, and contributed to writing, review, and editing. AG carried out histopathological interpretation, validation, and contributed to writing, review, and editing. AS contributed to clinical review, supervision, and writing, review, and editing. VK provided clinical oversight, contributed to writing, review, and editing, and gave final approval. SPK provided clinical oversight, contributed to writing, review, and editing, and gave final approval. All authors approved the final manuscript.

Data Availability

All relevant clinical information supporting the findings of this report is included within the manuscript. Additional de-identified details may be available from the corresponding author on reasonable request, subject to patient confidentiality.

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