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Dr. Dauod Arif for reviewing the pathology slides and Dr. Neha Mittal for assistance with IRB approval.

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The Utility of Fecal Calprotectin in the Diagnosis and Management of Microscopic Colitis

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Abstract

Background: **The incidence of microscopic colitis has increased over time. To date, there is no specific biomarker for microscopic colitis, and the diagnosis relies on histopathological tissue obtained during colonoscopy which is an invasive and costly procedure. Unlike Crohn's disease and ulcerative colitis, the utility of fecal calprotectin in diagnosing or monitoring microscopic colitis has not been established, and studies on the role of fecal calprotectin in microscopic colitis are limited. In this retrospective study, we analyzed the utility of this biomarker in the diagnosis of microscopic colitis.**

Methods: **The medical records of patients who have been diagnosed with collagenous colitis and lymphocytic colitis aged 18−89 years old were retrospectively reviewed. Patient characteristics were recorded in those who had fecal calprotectin measured.**

Results: **There were 198 patients who were diagnosed with collagenous colitis and lymphocytic between October 1, 2015, and July 31, 2022. Twenty-three patients had fecal calprotectin levels measured and were included in this study. The mean age was 51.7 ± 7.8 years in all groups. Thirteen patients were female. Six patients (26.1%) were diagnosed with collagenous colitis, and 17 patients (73.9%) were diagnosed with lymphocytic colitis. The fecal calprotectin cut-off in this lab is 50 μg/g stool. Median fecal calprotectin levels were 30.1 μg/g (15.6, 122.5), 19.5 μg/g (16.5, 64.6), and 33.2 μg/g (15.6, 134.9) in all groups, collagenous colitis, and lymphocytic colitis, respectively.**

Conclusion: **The utility of fecal calprotectin in diagnosing microscopic colitis is limited. Our study suggests the diagnosis should be based on histopathology tissue obtained during colonoscopy.**

Keywords: Fecal calprotectin, Microscopic colitis, Collagenous colitis, Lymphocytic colitis, Inflammatory bowel disease

1. Introduction

Microscopic colitis is an inflammatory bowel disease that is increasing in incidence.[1] The disease has a prevalence of 4 cases per 100,000. The mean age at diagnosis is between 60 and 65 years and is more common in females.[2] It is a common cause of chronic watery non-bloody diarrhea. To date, there is no specific biomarker for microscopic colitis, and the diagnosis relies on histopathological tissue obtained during colonoscopy which is an invasive and costly procedure. Microscopic colitis is classified into collagenous colitis and lymphocytic colitis.

Calprotectin is a protein derived from neutrophils. Measurement of fecal calprotectin is a useful marker for gastrointestinal inflammation and can be used to screen for inflammatory versus non-inflammatory gastrointestinal conditions, such as irritable bowel syndrome (IBS). It is particularly useful in diagnosis and monitoring inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis.[3] However, the utility of fecal calprotectin in diagnosing or monitoring microscopic colitis has not been established. More studies on the role of fecal calprotectin in microscopic colitis and the differentiation of microscopic colitis from IBS are needed. In this retrospective study, we analyzed the utility of

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this biomarker in the diagnosis of microscopic colitis.

2. Methods

A retrospective review was performed on patients aged 18–89 years who had been diagnosed with collagenous colitis or lymphocytic colitis between October 1, 2015, and July 31, 2022, at University Medical Center in Lubbock, TX. Data collected included age, sex, body mass index, comorbidities (including IBS and IBD), symptoms, duration of symptoms, indication for colonoscopy, diagnosis, pathology results, fecal calprotectin levels (on first diagnosis, during follow up visits, and in remission). Inclusion criteria included age 18–89 years old with the diagnosis of microscopic colitis unspecified, other microscopic colitis, collagenous colitis, and lymphocytic colitis based on ICD-10 codes of K52.839, K52.838, K52.831, and K52.832. All cases had confirmed histopathology from the colonoscopy. For patients with diagnosis of microscopic colitis unspecified and other microscopic colitis, the slide and pathology description were reviewed by pathologist who specialized in gastroenterology for the final diagnosis of collagenous colitis or lymphocytic colitis. Our exclusion criteria were patients with IBS and IBD and those who had fecal calprotectin ordered for other diagnoses. Fecal calprotectin values were determined using chemiluminescence enzyme-linked immunosorbent assays (ELISA). The cut-off level representing a positive value was $\geq$50 μg/g stool as stated by the manufacturer with values of 50–120 μg/g interpreted as borderline elevated, and values > 120 μg/g as elevated (normal <50 μg/g).

This study was approved by the Institutional Review Board for human research at Texas Tech University Health Sciences Center (L23-010). The primary aim of this study was to evaluate the utility of fecal calprotectin in diagnosing microscopic colitis and monitoring disease activity.

3. Results

One hundred and ninety-eight patients were diagnosed with collagenous colitis and lymphocytic colitis between October 1, 2015, and July 31, 2022 at University Medical Center, Lubbock, TX. Twenty-three patients had fecal calprotectin levels measured. The mean age was 51.7 ± 7.8 years (age range 22–79); 13 were female. Six patients (26.1%) were diagnosed with collagenous colitis, and 17 patients (73.9%) were diagnosed with lymphocytic colitis. Median fecal calprotectin levels in all group, collagenous colitis, and lymphocytic colitis were 30.1 μg/g (Q1:15.6 - Q3:122.5),19.5 μg/g (Q1:16.5 – Q3:64.6), and 33.2 μg/g (Q1:15.6 – Q3:134.9), respectively. Two patients (33.3%) in the collagenous colitis group and 10 patients (58.8%) in the lymphocytic colitis group had a fecal calprotectin >50 μg/g. In one patient, fecal calprotectin was measured twice. The initial fecal calprotectin was 84 μg/g, and the second was 31 μg/g after a relapse at 10 months after the patient had completed budesonide treatment for 3 months.

4. Discussion

All patients included in our study were between 22 and 79 years of age and had subacute to chronic watery non-bloody diarrhea for 2 weeks to 3 years in duration. The pathophysiology of microscopic colitis remains unclear and is likely multifactorial. Aberrant immune responses have been hypothesized as one potential explanation, since there is an increased risk of developing microscopic colitis in patients with autoimmune diseases, such as rheumatoid arthritis and thyroiditis.[2] Studies on potential biomarkers that can be used in diagnosing and monitoring microscopic colitis have been reported, but these biomarkers are not specific and largely reflect inflammatory bowel disease.[4] For example, the use of fecal calprotectin to differentiate IBS with diarrhea from IBD has a sensitivity and specificity of 93% and 96%, respectively.[5] A retrospective study by Batista reviewed adult patients who had colonoscopy to evaluate chronic non-bloody diarrhea.[6] Ninety-four patients with normal colonoscopies were included in the study, and 30 patients were diagnosed with microscopic colitis (13 collagenous colitis, 12 lymphocytic colitis, and five incomplete microscopic colitis). Sixty-four patients who were not diagnosed with microscopic colitis were in the control group and were diagnosed with self-limited or functional diarrhea. Fecal calprotectin was measured 2 weeks before colonoscopy. The median fecal calprotectin levels in microscopic colitis group and control group were 175 μg/g (Q1-Q3: 59–325 μg/g) and 28 μg/g (Q1-Q3: 16–111 μg/g), respectively (p-value = 0.0003).[6] Studies by Wildt and von Arnim have also reported a positive association between fecal calprotectin and active microscopic colitis.[6–8]

In our study, the fecal calprotectin varied in both collagenous colitis and lymphocytic colitis. Based on our study results, fecal calprotectin levels cannot be used to confirm the diagnosis of microscopic colitis in patients who present with chronic diarrhea. Normal fecal calprotectin levels do not exclude the possibility of microscopic colitis and the diagnosis of microscopic colitis should base on clinical and, more

importantly, histopathologic tissue obtained from colonoscopy. In terms of differentiating microscopic colitis and IBS, ROME IV diagnostic criteria should be applied before considering colonoscopy.[9]

Our limitation includes the fact that this is a retrospective study, and we could not compare the levels of fecal calprotectin in the microscopic colitis with the levels in healthy controls or in patients who present with chronic diarrhea but have different diagnosis after colonoscopy. This test might be useful in patients reluctant to undergo colonoscopy to decide about the need for a more invasive investigation since fecal calprotectin can be used in the settings of chronic diarrhea to differentiate the inflammatory bowel disease (ulcerative colitis, Crohn's disease, and microscopic colitis) from functional diarrhea, such as irritable bowel syndrome, but more studies on the natural history of diarrhea are needed to support this approach.

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Conflict of interest

None.

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