How to Treat Refractory Microscopic Colitis

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Learning objectives:

Upon completion of this session, the participant should be able to

1. Identify potential causes for refractory microscopic colitis
2. Describe the diagnostic approach to these patients
3. Understand treatment options

In approaching the question of how to treat the refractory microscopic colitis patient, it is important to define what is meant by this term. In its truest sense, this term would refer to microscopic colitis that does not respond to usual medical therapy, but it is important to note that recurrent or ongoing diarrhea in a patient with microscopic colitis is not always due to refractory disease, and in addition, this term is often applied to patients whose diarrhea recurs after an effective therapy is discontinued. Each of these three scenarios will be covered in this lunch break-out session.

Ongoing or Recurrent Symptoms in a Patient with Treated Microscopic Colitis

The differential diagnosis of ongoing or recurrent symptoms in a patient with microscopic colitis is broad and includes concomitant diagnoses such as post-inflammatory irritable bowel syndrome (PI-IBS) and inflammatory bowel disease (IBD), both of which have been reported in patients with microscopic colitis. As is true with other forms of colitis, microscopic colitis can be associated with ongoing abdominal discomfort and altered bowel habits due to PI-IBS even after the biopsies have normalized following treatment for microscopic colitis. Furthermore, several cases of IBD developing after a confirmed diagnosis of microscopic colitis have been reported. Another explanation for ongoing symptoms despite appropriate treatment for microscopic colitis is that the wrong diagnosis has been made. Although both lymphocytic and collagenous colitis have well accepted histologic criteria, occasionally a colonic biopsy will be misinterpreted. Colonic biopsies normally have inflammatory cells in the lamina propria, and sometimes this normal degree of inflammatory infiltrate is misinterpreted as a colitis. The presence of surface intraepithelial lymphocytosis, therefore, is a critical finding to confirm the diagnosis of microscopic colitis, particularly the lymphocytic colitis subtype. Another relatively common pitfall is the misinterpretation of a normal basement membrane that appears thickened due to tangential slicing of a mucosal biopsy which gives the false appearance of collagenous colitis. Given these possibilities, a patient with ongoing symptoms despite treatment should have their initial biopsies reread by an expert GI pathologist, and if the diagnosis is confirmed and symptoms continued despite appropriate therapy, then repeat biopsies should be obtained to assess for ongoing microscopic
colitis and to rule out additional diagnoses such as IBD. Normalization of the biopsies suggests that ongoing symptoms are due to PI-IBS, although microscopic colitis can be patchy and therefore the possibility of false-negative biopsies also needs to be considered. The risk of missing ongoing microscopic colitis should be reduced if at least 8 biopsies are taken from throughout the colon.

Another important explanation for ongoing or recurrent symptoms after appropriate treatment for microscopic colitis is the presence of concomitant celiac disease. Celiac disease is found in 10-15% or more of patients with microscopic colitis, and therefore, small bowel biopsies are recommended to evaluate a patient with ongoing symptoms despite appropriate therapy. Serologies may be considered as an alternate, but smaller older studies suggested that the sensitivity of serologies may be lower for celiac disease in patients with microscopic colitis compared to the general population. Another important entity to consider when evaluating a patient with refractory symptoms is drug-induced microscopic colitis. Several studies have reported statistically significant associations between microscopic colitis and a variety of medications including commonly prescribed drugs such as PPIs, SSRIs, and statins as well as prescription or over-the-counter NSAIDs. Therefore, a careful review of the medication list, including any over-the-counter medications, herbs or supplements, should be performed at the initial diagnosis of microscopic colitis as well as when evaluating any patient with refractory or recurrent symptoms.

In addition to these potential explanations for ongoing symptoms, other causes of diarrhea should also be considered including small intestinal bacterial overgrowth and pancreatic insufficiency. These diagnoses are seen infrequently but are relatively more common in older patients which is the demographic that most commonly has microscopic colitis. Another important consideration is medication noncompliance, especially with budesonide formulations which are commonly used to treat microscopic colitis, as these medications are expensive.

**Microscopic Colitis Refractory to Standard Therapy**

Several medications can be used to treat microscopic colitis. The evidence for mesalamine efficacy is limited, and therefore, nonresponse to this class of medication should not be considered refractory disease. Bismuth subsalicylate has been reported in small series and a very small placebo-controlled trial that has never been fully published. These studies suggest a role for bismuth in microscopic colitis, and a more recently study from Mayo suggested that bismuth may be particularly effective in patients with less severe diarrhea, especially if full dose (9 tablets/day) is used. However, the best treatment for microscopic colitis appears to be budesonide, and if the patient is refractory to bismuth, or if they have more severe diarrhea at presentation, they should be treated with this medication. Several randomized control trials in both collagenous and lymphocytic colitis have shown superiority of budesonide over placebo with response rates in the 80-90% range. If a patient is refractory to treatment with budesonide, then the potential explanations discussed above should be considered.
For patients who are truly refractory to full-dose budesonide, with no other explanation found and histologically confirmed ongoing active microscopic colitis, treatment with immunosuppressive medications is often considered. Bile acid binding medications have also been reported to be effective in small uncontrolled series and are often tried prior to the use of immunosuppressive medication. Small to medium case series have shown some efficacy for azathioprine, although one study reported a high rate of intolerance. Data on methotrexate and collaginous colitis is limited and conflicting. Finally, very small case series and anecdotal reports suggest a role for anti-TNF therapy in otherwise refractory microscopic colitis. The potential efficacy of anti-TNF medications in microscopic colitis needs to be balanced against what appears to be an increased risk of side effects in older patients treated with these medications, as derived from the IBD literature.

Recurrent Disease after Successful Therapy

Although bismuth and budesonide appear to be effective treatments for microscopic colitis, they often do not lead to permanent cure and symptoms may recur after therapy is stopped. Both treatments are recommended for an initial period of 8 weeks. In the early small open-label study of bismuth, the majority of patients maintain a lasting remission for months to years after that therapy was discontinued, and in the randomized control trials, patients that recurred often responded to a repeat course of bismuth. Concern about potential toxicity from long-term exposure to bismuth or salicylates, however, tempers the enthusiasm for ongoing chronic therapy with this drug. If symptoms can be controlled with infrequent courses, that is acceptable, but the need for ongoing maintenance should lead one to consider other therapies such as maintenance budesonide.

Although the response rate to budesonide is approximately 80-90%, most patients (70-80%) have a recurrence after budesonide is stopped. Therefore, recurrent disease after successful therapy is not unexpected. These patients are often treated with chronic low-dose maintenance budesonide, a practice that has been studied in at least three randomized controlled trials. Two of these studies induced remission with open-label budesonide and then maintained with 6 mg/day or placebo for six months. Both showed superiority of maintenance budesonide over placebo. Another more recent study used 6 mg/day alternating with 3 mg/day and also showed superiority over placebo. In practice, I recommend using the lowest effective dose that maintains remission, sometimes as low as 3 mg every other day. I typically treat patients for up to a year and then try a drug holiday to see if they need ongoing maintenance therapy or not. For patients who are treated chronically with budesonide, steroid-related side effects should be monitored for including hypertension, hyperglycemia, cataracts and other eye manifestations. I also typically check a bone densitometry at least once after a year of budesonide therapy, and if that is stable and normal, I usually do not continue to follow.

Steroid related side effects can be minimized by using the lowest effective dose and avoiding compounds that interfere with the P450 system including grapefruit, echinacea, and several medications.
In summary, when considering a patient with “refractory microscopic colitis”, one must define what that means. Recurrent disease after successful therapy is not unexpected and can usually be managed with maintenance therapy. Ongoing symptoms despite therapy should prompt an assessment for alternate diagnoses such as post-inflammatory IBS, concomitant celiac disease, or ongoing consumption of a medication that might be driving the colitis such as PPIs, SSRIs, statins, and NSAIDs. Finally, truly refractory disease usually can be managed with a bile salt binder or various immune suppressing medications in most patients. Surgery for refractory disease is needed in <1% of patients.