Microscopic colitis encompasses two distinct conditions that cause chronic watery, non-bloody diarrhea without obvious endoscopic findings. Diagnosis is not always straightforward and many times requires a biopsy of colonic mucosa. Its vague presentation is similar to celiac disease, irritable bowel syndrome (IBS), or inflammatory bowel disease (IBD). The diagnosis of microscopic colitis can be complicated further with concurrent celiac disease or IBD. Treatment is usually aimed at shortening the duration of symptoms. In this paper we will discuss current methods of diagnosis, confounding issues, and treatment.

INTRODUCTION

The term microscopic colitis encompasses two separate diagnoses: lymphocytic colitis and collagenous colitis. The names describe the change to the colonic mucosa that is not due to an infectious cause, ultimately causing chronic watery, non-bloody diarrhea without other physical findings. It affects women more commonly than men and presents usually above the age of 65. Microscopic colitis can be confused with diseases that present similarly, such as celiac disease, IBS or IBD.

A colonoscopy is often normal and biopsies of the colonic mucosa are required to make a definitive diagnosis. It is easy to distinguish collagenous colitis from lymphocytic colitis by the presence of a thick subepithelial collagen band whereas the telltale sign of lymphocytic colitis is infiltration of the colonic epithelium with lymphocytes. The two conditions under the umbrella of microscopic colitis have an association with other autoimmune disorders like celiac disease, rheumatoid arthritis, thyroid disease or diabetes mellitus. In patients with concurrent celiac disease or IBD, the diagnosis of microscopic colitis is often difficult. The goal of treatment is to shorten the duration and control symptoms and can be accomplished successfully in most cases. In this paper we will discuss current methods of diagnosis, confounding issues, and treatment.
Definition
Microscopic colitis is defined by symptoms of chronic, watery diarrhea without identification of an infectious cause, often without endoscopic lesions or radiographic findings but only with histologic abnormalities.3, 7

Epidemiology
With increased awareness and improved diagnostic capabilities, microscopic colitis has become a common diagnosis. The incidence of microscopic colitis is 10/100,000 in the United States.4 Lymphocytic colitis is slightly more prevalent and has a 5.5/100,000 incidence,5 whereas collagenous colitis currently has an incidence of 4.6/100,000.6 The average age of diagnosis in microscopic colitis is 60-65 and patients older than 65 have five times the risk of developing microscopic colitis.6 The other risk factors for developing microscopic colitis include female gender, personal history of malignancy, hypothyroidism or celiac disease.6

Pathogenesis
The etiology is multifactorial and the exact mechanism remains unknown. However, it is believed that a dysregulated immune response to a luminal agent leads to reduced sodium and chloride absorption as well as active chloride secretion.7 The diarrhea can be defined as secretory. One study showed that the thick collagen band found in collagenous colitis may act as a diffusion barrier and down-regulate tight junction molecules.8 Medications that have been implicated in causing microscopic colitis include H2 blockers, PPI, SSRI’s, carbamazepine, simvastatin, and ticlopidine.9 10, 11 Lansoprazole, for example, a potent and commonly used PPI has been extensively studied for its association with microscopic colitis.12,13,14 A case study of 850 patients who were switched from omeprazole to lansoprazole showed direct correlation of lansoprazole with intermittent diarrhea characterized as lymphocytic and collagenous colitis on histology. When lansoprazole was discontinued, follow-up biopsies revealed resolution with normalization of colonic histology.15

Clinical Findings
Symptoms may include some or all of the following: intermittent or persistent watery diarrhea, abdominal cramps, fecal urgency or incontinence, weight loss, or nausea. A complete history helps differentiate this disease from other causes of chronic, watery diarrhea. It

(continued on page 18)
Diagnosis and Management of Microscopic Colitis

(continued from page 13)

is important to obtain a thorough medication list, which includes both prescription and over-the-counter drugs. Physical exam is usually unremarkable.

Laboratory markers are generally not useful for the diagnosis or for assessing disease activity. A stool sample should be collected as a first step. Although not routinely used for diagnosis, there are an increased number of CD3+ T cells found in the lamina propria and intraepithelial compartments in both lymphocytic and collagenous colitis.16, 17 There are no specific autoantibodies implicated as markers for microscopic colitis.18 Autoantibodies against GnRH or GnRH-R, seen in IBS are not frequently observed in microscopic colitis patients.19 Interestingly, there is an increased incidence of HLA DQ2 in both subtypes of microscopic colitis.

Diagnostic Modalities (Table 1)
The test of choice is a colonoscopy with biopsies. Histology of colonic biopsies which show inflammation of the mucosa and thickening of the subepithelial collagen layer, as in collagenous colitis, or an increase in the number of lymphocytes in the surface epithelium as in lymphocytic colitis.20 Flexible sigmoidoscopy may be sufficient; however, negative findings do not exclude the possibility of this disease.21 It is important to take multiple biopsies throughout the colon, as collagenous and lymphocytic colitis may be patchy. However, greater than 90% of findings are present in the left colon.22, 23, 24

Endoscopy and Pathology
Colonoscopy is usually grossly normal (figure A). However, a coarse and nodular surface of the mucosa may be seen in collagenous colitis. Erythema and tortuous vasculature with diffuse cloudiness of the mucosa have been noted in early development of collagenous colitis.25 Mild edema and loss of vascularity can be seen (figure B). A “cat-scratch” appearance of the colonic mucosa may occur in collagenous colitis, further defined as “mucosal tears” (figure C).26 This finding is explained by the barotrauma in the colon with decreased compliance due to the rigidity of collagen in the subepithelium. Histologically, collagenous colitis is described by colonic mucosal subepithelial collagen deposits 7-100 micrometers in diameter (figure D) (normal being 1-7 micrometers). Subepithelial collagen layer that is greater than 10 micrometers is a common finding. Lymphocytic colitis is characterized by mononuclear infiltrates with few neutrophils and eosinophils in the lamina propria and intraepithelial lymphocytes greater than 20 per 100 surface epithelial cells (figure E) (normal are 3-5/100 cells). Focal cryptitis (figure F) is sometimes present. Epithelial damage, such as cellular flattening and mucin depletion may occur.27

Diagnostic Dilemmas and Associations with the Disease (Table 2)
Microscopic colitis may be diagnosed in patients with concomitant IBS, IBD or celiac disease. Others include chronic ischemia or infectious colitis, hyperthyroidism, carcinoid, VIPoma, or persistent NSAID. A ‘quick way’ to distinguish chronic diarrhea in a patient with microscopic colitis from a patient with IBD is the preserved mucosal architecture.28 One study found that there is a 70-fold increase in risk for an individual with celiac disease to develop microscopic colitis when compared with the general population.27 Concomitant celiac disease is present in approximately 5% of the patients with microscopic colitis.29 IBD may have focal areas of microscopic colitis. It is more common to have concurrent autoimmune disease, including celiac disease, with collagenous colitis as compared to lymphocytic colitis (53% to 26% respectively).30 Distinguishing celiac disease from microscopic colitis requires serological tests, such as anti-tTG antibodies.31, 33 Collagenous...
Inflammatory bowel disease: a practical approach, series #87

Colitis must be differentiated from ischemic colitis, as both will demonstrate a thickening of the connective tissue band, seen with a three-color histologic staining protocol, Masson’s trichrome. Collagenous colitis may be a systemic autoimmune disorder with extraintestinal manifestations such as arthritis and thyroiditis. A Duke study revealed an association between seronegative spondyloarthropathy with collagenous colitis in 7% of patients with confirmed collagenous colitis. There is an increased relative risk of lung cancer in women with collagenous colitis. Smoking and chronic alcohol use have been implicated as risk factors for development of microscopic colitis.

Management Goals and Treatment
Quality of life is directly proportional to disease activity in patients with microscopic colitis. Clinical remission is not always associated with histological remission and relapses are common. The goal of pharmacological treatment is to improve symptoms while minimizing side effects. A treatment algorithm is outlined in Figure F. Prior to initiating pharmacological treatment, it is important to remove any drugs that may be contributing to symptoms. Next, associated conditions should be properly managed. Dietary modifications are helpful in those patients who notice an association between certain foods. However, patients with isolated microscopic colitis, sans celiac disease, do not adequately respond to dietary gluten withdrawal. Symptomatic treatment with antidiarrheal agents such as loperamide is appropriate. Colloidal bismuth, cholestyramine, sulfasalazine, and mesalamine may be added if diarrhea is not controlled. Failing these patients require systemic steroids, but...
thickening in the colonoscopic mucosa. These diseases are thought to be autoimmune in origin and have associations with celiac disease, thyroid disease, and diabetes mellitus. The etiology still remains unclear. Goals of treatment remain the elimination of exacerbating factors and controlling symptoms.

**SUMMARY**

Lymphocytic colitis and collagenous colitis can be both categorized under the general umbrella of microscopic colitis. Clinical symptoms include chronic, non-bloody, watery diarrhea and histologic findings of lymphocytic proliferation or collagen

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22