

## Colonic Mimics of Inflammatory Bowel Diseases

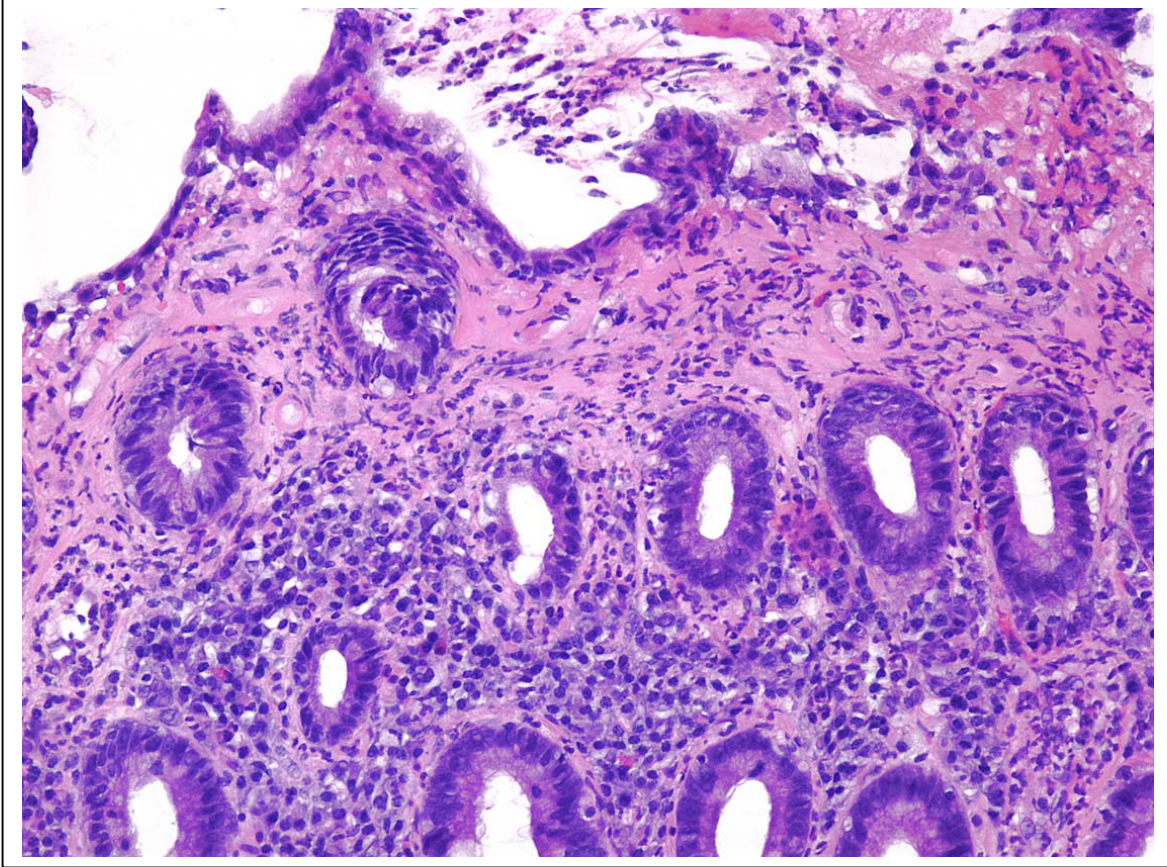
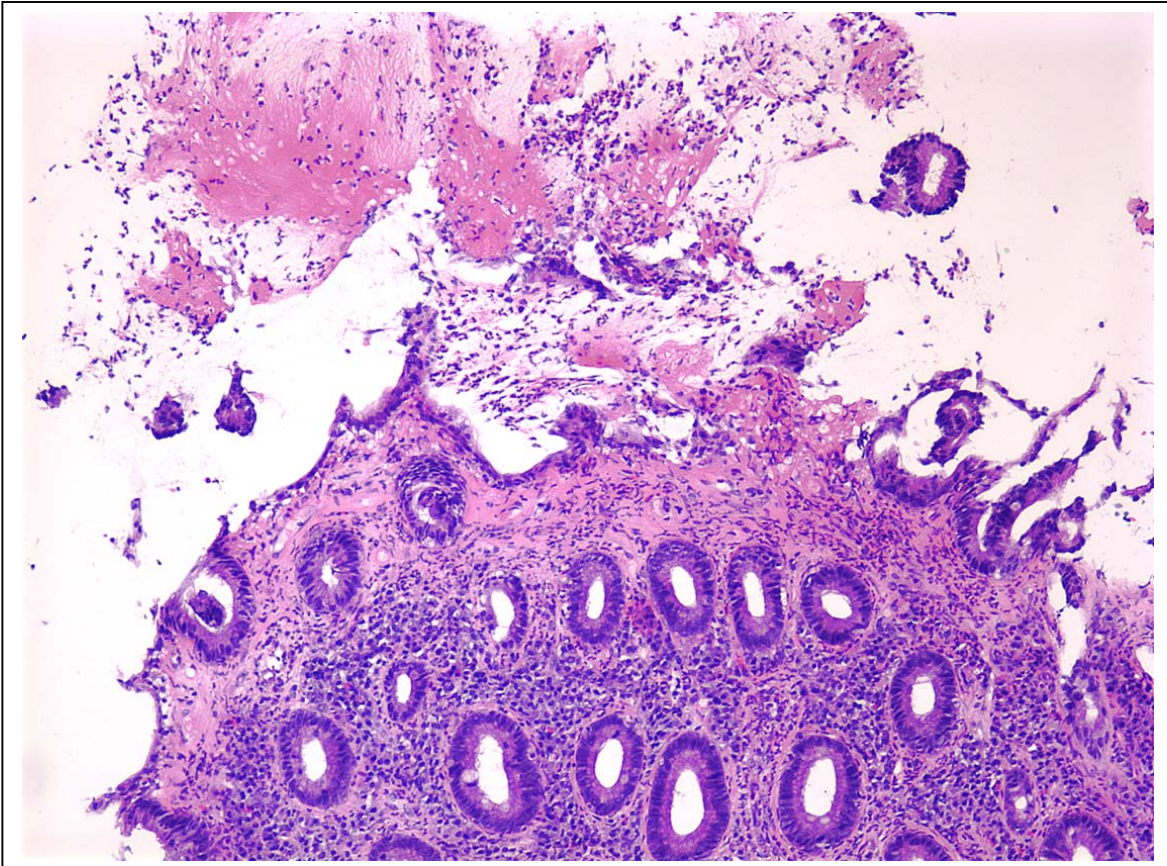
Susan C. Abraham, M.D

Case Illustration: Collagenous colitis, a potential mimic of ulcerative colitis and infectious colitis

This 69-year-old woman complained of having up to 20 watery bowel movements per day, associated with urgency, fecal incontinence, and significant (35 pounds) weight loss. She also complained of crampy abdominal pain and had noticed some blood (both dark and bright red) in her stools, occurring about twice a week.

Colonoscopy was performed and showed mild edema on the right side. The transverse and left colon showed more significant edema, areas of friability, and tenacious yellowish “mucus” throughout the entire left side. There were no ulcerations.

Stool cultures were negative. Stool toxin assay for *C. difficile* was positive.



## **Pseudomembranous collagenous colitis (associated with *C. difficile*)**

### **Pathologic features of lymphocytic colitis and collagenous colitis:**

The term "microscopic colitis" is frequently used by gastroenterologists to describe patients who have chronic watery diarrhea, normal or near-normal endoscopic findings, and a spectrum of histologic abnormalities that includes increased numbers of intraepithelial lymphocytes. We do not use the term "microscopic colitis" as a pathologic diagnosis. Instead, these cases are categorized as either lymphocytic colitis or collagenous colitis.

Both lymphocytic colitis and collagenous colitis share several common histologic abnormalities:

1) Chief among these is an increased number of lymphocytes in the colonic epithelium. The normal colonic epithelium contains only approximately 5 lymphocytes per 100 epithelial cells. In both lymphocytic and collagenous colitis, this number is increased (definitionally, *increased* is considered to be >15-20 lymphocytes per 100 epithelial cells). These are CD3+, predominantly CD8+ T-cells. They are most noticeable, and are typically counted in, the surface epithelium; however, in most cases the lymphocytosis can also be appreciated in the cryptal epithelium. One important caveat in assessing the number of intraepithelial lymphocytes is not to count over a lymphoid follicle.

2) In both lymphocytic and collagenous colitis, there is increased cellularity of the lamina propria which is due to increased lymphoplasmacytic inflammation in the superficial lamina propria.

3) Typically, the surface epithelium is "injured" -- that is, flattened and disorganized-appearing.

How do lymphocytic and collagenous colitis differ histologically? In lymphocytic colitis, the basement membrane and subepithelial collagen layer are normal. In collagenous colitis, the basement membrane itself is normal, but the subepithelial collagen layer is thickened and abnormal. Normally, this layer is only 5-6 microns; in collagenous colitis it is usually >12-15 microns. This increase is due to deposition of mature type I and type III collagen. However, we do not use the absolute thickness as the sole diagnostic feature for collagenous colitis. This is because: 1) In tangentially embedded biopsies, the collagen layer can appear thicker than it actually is. 2) Swelling of the true basement membrane, as not infrequently occurs in biopsies from the distal colon, will show a thick layer beneath the surface epithelium; however, this thickened layer is basement membrane material rather than subepithelial collagen, and it differs from true subepithelial collagen thickening in that it is very sharply demarcated from the underlying lamina propria. 3) In early or patchy collagenous colitis, the absolute thickness of the subepithelial collagen layer may not exceed 12-15 microns, but it will show other more diagnostically important abnormalities. These consist of irregularity of the basal aspect so that the collagen seems to "drip down" into the lamina propria, and abnormal incorporation of capillaries and inflammatory cells into the collagen.

What is the proper biopsy technique to diagnose lymphocytic or collagenous colitis? This issue arises when a patient presents with watery diarrhea symptoms and the clinician performs a limited colonoscopy with only rectosigmoid biopsies. If these biopsies are "normal," the possibility of collagenous colitis has not been ruled out and pancolonoscopy with multiple biopsies may be needed. In a series from the Mayo Clinic, Carpenter *et al* reviewed biopsies throughout the GI tract in 14 patients with collagenous colitis. They found that rectosigmoid biopsies are often normal in collagenous colitis and therefore underestimate that diagnosis. In

40% of their patients, proctosigmoidoscopic examinations alone would have missed the diagnosis of collagenous colitis. Tanaka et al examined the utility of left sided biopsies in collagenous colitis. They first examined the colonic geographic distribution of collagenous colitis in order to assess the utility of flexible sigmoidoscopy. They found that rectal biopsies showed no increase in collagen layer in 73% of patients with documented collagenous colitis. In approximately one-third of cases in which rectal biopsies showed no increased collagen layer, there was as well a lack of increased chronic inflammation. On the other hand, flexible sigmoidoscopy with multiple left sided biopsies did show at least increased chronic inflammation in 70% of cases. Thus, a patient presenting with watery diarrhea due to collagenous colitis is very likely to have a rectosigmoid biopsy showing normal crypt architecture with increased chronic inflammation. Pancolonoscopy with multiple right sided biopsies should then prove diagnostic. Additionally, Tanaka *et al* found the collagen layer to be patchy and not continuous; thus, multiple biopsies may be needed to detect this change. We have also observed a trend toward decreasing numbers of intraepithelial lymphocytes in distal colorectal biopsies in patients with lymphocytic colitis, but this is usually not as pronounced as in collagenous colitis.

What are the differences between lymphocytic colitis and collagenous colitis?

Both lymphocytic and collagenous colitis have virtually indistinguishable clinical presentations. The typical patient is a middle-aged to older female who has had prolonged, watery diarrhea. Stool cultures are usually negative. The watery stools do not dramatically decrease with fasting and are not bloody; thus, patients are classified as having a secretory diarrhea. The collagen layer itself is not thought to play a prominent mechanistic role in the diarrhea; the severity of diarrhea has been shown to be proportional to the degree of chronic inflammation and not the thickness of the collagen layer. The diarrhea is secretory and electrophysiologic studies have shown active anion secretion (chloride) with sodium following passively (Rask-Madsen *et al*, 1983). The role prostaglandins play is unclear. Patients may present with vague abdominal pain and a weight loss of 10-15 lbs. Prior to the description of lymphocytic and collagenous colitis, these patients were frequently classified as having a psychosomatic illness or irritable bowel syndrome.

It is not clear whether lymphocytic and collagenous colitis are manifestations of a single disease or whether they are distinct but overlapping syndromes. In a 1999 article in *Gut*, Baert *et al* reviewed 96 patients with collagenous colitis and 80 patients with lymphocytic colitis. The average age at diagnosis was ~64 years for both groups. Patients with collagenous colitis were much more likely to be women (M:F ratio of 27:73) whereas there was a more even sex distribution in lymphocytic colitis (M:F ratio of 45:55). Patients with collagenous colitis were more likely to be active smokers (25% vs. 14%). The overall prognosis of disease was good in both groups, although patients with lymphocytic colitis tended to have somewhat milder symptoms and were slightly more likely to report resolution or significant improvement in their symptoms (84%) than were patients with collagenous colitis (74%). They concluded, as have others, that lymphocytic and collagenous colitis are similar but not identical diseases.

#### **Associations/etiologies for lymphocytic and collagenous colitis:**

- Drugs/medications, including NSAIDs, ticlopidine, lansoprazole, flutamide, and herbal preparations. Wang *et al* found that 20/40 (50%) of patients with lymphocytic colitis were using NSAIDs at the time of their colonic biopsies. In a 1997 review, Goff *et al* found that 22/31 (71%) of patients with collagenous colitis were using NSAIDs regularly at the time of diagnosis, and in 3 patients resolution of symptoms occurred with

discontinuation of the NSAIDs. Yagi *et al* (2001) demonstrated clinical and histologic resolution of collagenous colitis in a 77-year-old woman. Riddell *et al* (1992) showed that long-term NSAID use was significantly more common in patients with collagenous colitis (19 of 31 patients) than in a matched control group of patients with irritable bowel syndrome or diverticular disease (only 4 of 31 controls), and that in 3 patients the diarrhea improved after withdrawal of NSAIDs. In the study of 176 patients cited above by Baert *et al*, the authors identified cases of lymphocytic or collagenous colitis that were temporally related to ticlopidine (6 cases), flutamide (4 patients), and herbal medications (2 patients), all of which resolved without other therapy on discontinuation of the drugs.

- Celiac disease. Lymphocytic colitis is a frequent finding in patients with celiac disease, with estimates ranging from 11% to 31% of celiac patients. In Wang's study of lymphocytic colitis/colonic lymphocytosis patients, 16 patients had small bowel biopsies for review and celiac sprue-like changes were seen in 3/16 (19%). Matteoni *et al* (*J Clin Gastroenterol* 2001) identified celiac-like changes in small bowel biopsies from 4 of 27 patients with lymphocytic colitis (15%), but not in any of the patients with collagenous colitis (0 of 19, 0%). Gillett and Freman (*Can J Gastroenterol* 2000) studied the prevalence of celiac disease in patients with lymphocytic and collagenous colitis using IgA anti-endomysial antibody titers and IgA against tissue transglutaminase (tTG). They found that 4 of 15 (27%) patients with lymphocytic colitis had either new (1 patient) or previously diagnosed (3 patients) celiac disease, whereas none of 8 (0%) patients with collagenous colitis had serologic evidence of celiac disease. However, isolated reports of patients with both collagenous colitis and celiac disease do exist (e.g., O'Mahony *et al* 1990, Hamilton *et al* 1986, Breen *et al* 1987).
- Crohn's disease. Goldstein and Gyorfi (*Am J Surg Pathol* 1999) described 5 patients with Crohn's disease whose colonic biopsies showed changes resembling either lymphocytic colitis (4 patients) or collagenous colitis (1 patient). However, in 4 of 5 cases these changes were focal only, and in 3 cases separate biopsies from either the terminal ileum or elsewhere in the colon showed more typical changes of Crohn's disease. We therefore believe that it is a rare event that cases appearing histologically typical for lymphocytic or collagenous colitis later prove to have Crohn's disease. This distinction is important because patients with lymphocytic colitis and collagenous colitis are not at increased risk for epithelial dysplasia or adenocarcinoma and do not require routine colonoscopic surveillance, whereas patients with Crohn's disease or ulcerative colitis do.

#### **“Pseudomembranous collagenous colitis”:**

Recently, Yuan *et al* (*Am J Surg Pathol* 2003) reported 10 patients with collagenous colitis and pseudomembranes. In addition to pseudomembrane formation, there was mild neutrophilic cryptitis seen in 42% of the biopsies. In contrast to most patients with collagenous colitis, the endoscopic appearance of the colon was abnormal in 7 cases and included ulcers (5 cases), erythema (2 cases), and inflammation (1 case); in fact, 6 patients were endoscopically suspicious for Crohn's disease or ulcerative colitis. An etiology for the pseudomembrane formation was identified in only one of their 10 cases, a patient with *C. difficile* colitis. However, stool cultures for pathogenic organisms were performed in only 4 cases, *C. difficile* toxin assay in only 6 cases, and evaluation for *E. coli* O157:H7 in only 3 cases. None of the 10 patients had evidence for ischemia. Overall, the clinical outcome of the 10 patients in that study did not differ from typical collagenous colitis without pseudomembranes.

This study indicates that, although perhaps infrequently, *C. difficile* colitis can co-exist with collagenous colitis and it is important to recognize both processes histologically. Other cases reports support the occasional association between the two diseases. For example, Khan *et al* (*Dig Dis Sci* 2000) described an 89-year-old woman with collagenous colitis who had three episodes of pseudomembranous colitis related to *C. difficile* infection; each episode resolved with a course of vancomycin.

### **Cryptitis and crypt abscesses in collagenous colitis**

Ayata *et al* (*Am J Surg Pathol* 2002) reported active inflammation to be a relatively common finding in collagenous colitis, present in 24 of 79 cases (30%) in their series. Four patients (5%) had crypt abscesses, and 2 (2.5%) had surface ulcers. One of the patients with active inflammation in that study was positive for *Salmonella* on stool culture. Cryptitis also correlated significantly with recent antibiotic use, but unfortunately none of the patients in that study had stool toxin assays performed to evaluate for *C. difficile*.

In a study reported in abstract form (*Mod Pathol* 2000), we reviewed the pathology reports from 266 cases of collagenous colitis at The Johns Hopkins Hospital between 1989 and 1999. 37 of 266 (14%) had severe active inflammation (mucosal erosion/ulcer or crypt abscesses), 91 of 266 (34%) had low-grade active inflammation (mild cryptitis or surface intraepithelial neutrophils), and 138 of 266 (52%) had inactive collagenous colitis. In a subset of patients, the endoscopic findings and clinicopathologic features were reviewed. Patients with severely active collagenous colitis were more likely to have abnormal endoscopic findings (14 of 16, 88%) than patients with low-grade active (8 of 27, 30%) or inactive (3 of 27, 11%) collagenous colitis. They were also more likely to have heme + stool (6 of 13, 46%). A superimposed etiology for the active inflammation was found in 4 of 17 patients with severely active collagenous colitis (including 1 patient with *Aeromonas* infection, 1 with *C. difficile* infection, 1 with colonic ischemia, and 1 with NSAID-induced colonic ulcer) and in 4 of 17 patients with low-grade active collagenous colitis (3 with recently treated *C. difficile* colitis and 1 with recently treated *C. jejuni*), but in none of 15 patients with inactive collagenous colitis.

Unless there is significant crypt architectural distortion or basal plasmacytosis to suggest ulcerative colitis, we diagnose such cases as collagenous colitis with a note indicating that the degree of active inflammation could reflect a superimposed infectious colitis or other inflammatory etiology, so that appropriate clinical work-up is initiated.

### **References:**

- 1 Abraham S, Yardley JH, Wu TT: Significance of active inflammation in collagenous colitis: clinical and endoscopic correlates. *Mod Pathol* 13:75A, 2000.
- 2 Ayata G, Ithamukkala S, Sapp H, Shaz BH, et al: Prevalence and significance of inflammatory bowel disease-like morphologic features in collagenous and lymphocytic colitis. *Am J Surg Pathol* 26:1414-23, 2002.
- 3 Baert F, Wouters K, D'Haens G, et al: Lymphocytic colitis: a distinct clinical entity? A clinicopathological confrontation of lymphocytic and collagenous colitis. *Gut* 45:375-381, 1999.
- 4 Breen EG, Farren C, Connolly CE, McCarthy CF: Collagenous colitis and coeliac disease. *Gut* 28:364, 1987.

- 5 Carpenter HA, Tremaine WJ, Batts KP, Czaja AJ. Sequential histologic evaluations in collagenous colitis. Correlations with disease behavior and sampling strategy. *Dig Dis Sci* 37:1903-9, 1992.
- 6 Gillett HR, Freeman HJ: Prevalence of celiac disease in collagenous and lymphocytic colitis. *Can J Gastroenterol* 14:919-921, 2000.
- 7 Goff JS, Barnett JL, Pelke T, Appelman HD: Collagenous colitis: histopathology and clinical course. *Am J Gastroenterol* 92:57-60, 1997.
- 8 Goldstein NS, Gyorfi T: Focal lymphocytic colitis and collagenous colitis. Patterns of Crohn's colitis? *Am J Surg Pathol* 23:1075-1081, 1999.
- 9 Hamilton I, Sanders S, Hopwood D, Bouchier IA: Collagenous colitis associated with small intestinal villous atrophy. *Gut* 27:1394-1398, 1986.
- 10 Khan MA, Brunt E, Longo WE, Presti ME: Persistent *Clostridium difficile* colitis: a possible etiology for the development of collagenous colitis. *Dig Dis Sci* 45:998-1001, 2000.
- 11 Loftus EV. Microscopic colitis: epidemiology and treatment. *Am J Gastroenterol* 98:S31-S36, 2003.
- 12 Matteoni CA, Goldblum JR, Wang N, et al: Celiac disease is highly prevalent in lymphocytic colitis. *J Clin Gastroenterol* 32:225-227, 2001.
- 13 O'Mahony S, Nawroz IM, Ferguson A: Coeliac disease and collagenous colitis. *Postgrad Med J* 66:238-241, 1990.
- 14 Rask-Madsen J, Grove O, Hansen MGJ, Bukhave K, Scient C and Henrik-Nielsen R: Colonic transport of water and electrolytes in a patient with secretory diarrhea due to collagenous colitis. *Digestive Diseases and Sciences* 28(12):1141-1146, 1983.
- 15 Riddell RH, Tanaka M, Mazzoleni G: Non-steroidal anti-inflammatory drugs as a possible cause of collagenous colitis: a case-control study. *Gut* 33:683-686, 1992.
- 16 Tanaka M, Mazzoleni G and Riddell RH: Distribution of collagenous colitis: utility of flexible sigmoidoscopy.
- 17 Wang N, Dumot JA, Achkar E, et al: Colonic epithelial lymphocytosis without a thickened subepithelial collagen table. A clinicopathologic study of 40 cases supporting a heterogeneous entity. *Am J Surg Pathol* 23:1068-1074, 1999.
- 18 Wilcox GM, Mattia A: Collagenous colitis associated with lansoprazole. *J Clin Gastroenterol* 34:164-166, 2002.
- 19 Yuan S, Reyes V, Bronner MP. Pseudomembranous collagenous colitis. *Am J Surg Pathol* 27:1375-9, 2003.