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COLLAGENOUS COLITIS

General Comments: Collagenous colitis is a clinicopathologic syndrome characterized by (1) chronic watery diarrhea and crampy abdominal pain and (2) distinctive colorectal histopathology that includes a subepithelial collagen band, prominent chronic inflammation in the lamina propria, and increased intraepithelial lymphocytes. In 1976, Lindstrom described the first case. Lindstrom coined the term *collagenous colitis* because of the histopathologic similarity to collagenous sprue, in which a collagen deposit is seen in a similar subepithelial location but in jejunal mucosa. Several studies have addressed the prevalence of collagenous colitis. In persons with chronic diarrhea, the frequency of collagenous colitis ranges from 0.3% to 5.0%. The incidence of this disorder has been estimated to range from 1.8 to 5.2 cases per 100,000 population. This disease is found mainly in “Western” countries in Europe, Australia, and North America, but rare cases have been reported from Japan and Africa.

Pathologic Features: As the name implies, there are two main histologic components to collagenous colitis: (1) increased collagen deposition and (2) colitis. A main histologic component is the presence of increased subepithelial collagen. The increased collagen can be recognized on conventional hematoxylin and eosin stains as an eosinophilic band localized just beneath the surface epithelium and has been reported to contain collagen of many types. Recent reports show primarily types I, III, and VI collagen, and tenascin. In normals, the subepithelial basement membrane is no greater than 3 μm but can be thicker in hyperplastic polyps and with tangential sectioning. In collagenous colitis, the width of the band averaged 15 μm in one series. In many patients, band thickness varies throughout the colon with the transverse colon usually having the thickest bands. The rectum can lack a thick subepithelial collagen band in up to 25% of cases and in a small percentage, the rectum can be normal with no increase in inflammation. Consequently, multiple biopsy specimens should be taken in areas proximal to the rectosigmoid sampled to establish or exclude the diagnosis of collagenous colitis. In rare cases, subepithelial collagen has also been noted in duodenal and gastric mucosa in patients with collagenous colitis.

The increased subepithelial collagen has qualitative and quantitative changes from normal colon. In normal colonic epithelium, the basement membrane has sharp, well-defined edges. In collagenous colitis, the increased collagen imparts a shaggy appearance to the lower border of the basement membrane with tendrils of collagen extending down into the upper lamina propria. To delineate mild increases in subepithelial collagen, a trichrome stain is helpful. Immunoperoxidase stains for tenascin have also been touted as a sensitive and specific marker for the subepithelial collagen band. Any increase in subepithelial collagen, in the proper inflammatory and clinical context, is diagnostic of collagenous colitis. Hence, measurement of the thickness of subepithelial collagen layer is not necessary to diagnose collagenous colitis.

The second histologic component in collagenous colitis involves increases in inflammation both in the lamina propria and within the epithelium. The lamina propria is expanded by a mixture of inflammatory cells, including plasma cells, lymphocytes, eosinophils, and mast cells. Increased eosinophils can be striking in some cases. Eosinophil granule component as well as TGF beta made by the eosinophils, may be involved in the pathophysiology of the disease. Crypt distortion is rare, but Paneth cell metaplasia is not uncommon, and a sprinkling of neutrophils can be seen in up to 25% of case. Extensive neutrophils and pseudomembranes are rare but have been described in a few cases, potentially in acute or early stage of the illness or concomitant *C. difficile* infection.

A distinctive component of collagenous colitis is increased intraepithelial lymphocytes. An increase in these cells is present in the majority, but not all, cases of collagenous colitis. Prominent intraepithelial lymphocytes are not a feature of other forms of colitis or enteritis except for celiac disease and lymphocytic colitis. The intraepithelial lymphocytes of collagenous colitis are predominantly CD8+ T cells and express the alpha beta form of the T cell receptor. Surface epithelial damage (flattening, detachment) may also be present.

Misdiagnosis of collagenous colitis can occur by focusing exclusively on the thickness of the subepithelial collagen band. Collagenous colitis is an *inflammatory* disorder of the colon, and thus

increased mucosal inflammation is a prerequisite to the diagnosis. The basement membrane can appear artificially increased in size. For example, tangential sectioning of the basement membrane creates a thicker basement membrane than when correctly oriented.

Pathogenesis: The cause of collagenous colitis is unknown, and thus it can be considered a type of chronic idiopathic IBD, albeit of a “gentler and more subtle form.” Hypotheses for the etiology of collagenous colitis include (1) immune dysregulation, (2) abnormalities in pericryptal fibroblasts, (3) intraluminal bacterial agents or toxins, (4) plasmatic vasculosis, and (5) drug induced damage.

Some of the most intriguing recent findings relate to the possible role of infectious agents in collagenous colitis. Swedish investigators found that diverting the fecal stream caused clinical and histological remission in nine patients and that clinical symptoms and an abnormal collagen table returned after ostomy takedown. This, of course, suggests that some luminal agent or toxin is involved. Some investigators have found clinical improvement in patients treated with antibiotics or with bismuth subsalicylate, an agent thought to work via an antibacterial mechanism. Also, antibodies against *Yersinia* virulence factors are more common in collagenous colitis than in control patients. The pattern of inflammation, with increased intraepithelial lymphocytes, suggests polarization of the immune system toward a luminal agent. One hypothesis is that a foreign luminal agent, possibly bacteria, initiates colorectal inflammation that leads to an immunologic cross-reactivity with an endogenous antigen in luminal epithelial cells leading to a self sustaining inflammatory condition.

On the other hand, collagenous colitis has been linked in rare cases to lansoprazole administration, (the association is more common with lymphocytic colitis.) In these cases, drug was clearly associated with onset of symptoms and resolved with lansoprazole was stopped. NSAIDs have also been linked to collagenous colitis by a few investigators but not others.

The mechanisms of diarrhea are variable between patients. Fasting improves, but does not totally abate the diarrhea in most patients, suggesting both an osmotic and a secretory component to the diarrhea. Reduced Na and Cl absorption are the main mechanisms of diarrhea in collagenous colitis, but there is also an active component of Cl secretion. Down regulation of tight junction molecules, particularly occludin, is thought to contribute to the diarrhea. While the diarrhea is felt to be mainly of colonic origin, some studies have also shown abnormal permeability in the small bowel as well.

Clinical History: Collagenous colitis is a disease primarily of women with a female to male predominance of nine to one. This disorder is seen primarily in middle-aged patients with a mean age of diagnosis of 59 years, but a wide age range of presentation. No well documented cases have been described in children.

Chronic watery diarrhea is the main symptom and in most patients has been present months to years. Nocturnal diarrhea is not uncommon. The patients often also have crampy diffuse abdominal pain, symptoms which cause misdiagnosis with irritable bowel syndrome. Enteropathic arthritis is seen in approximately 7% of collagenous colitis patients, with the arthritis being seronegative for rheumatoid factor and nondestructive. A variety of other immunologic disorders have been noted in this patient population, with 17%-40% of patients having coexistent autoimmune illnesses.

Routine laboratory studies are usually normal. However, antineutrophilic cytoplasmic antibodies have been described. Importantly, gastrointestinal radiographic and endoscopic examinations usually show normal mucosa. Thus, it is essential for clinicians to biopsy grossly normal mucosa to establish this diagnosis.

Treatment: While collagenous colitis is usually a chronic process, patients can have spontaneous remissions, thus complicating evaluation of drug effectiveness. While dietary modification (elimination of caffeine, lactose, or NSAIDs) may help some individuals, most require medication of some sort. In the past, first line therapy was with sulfasalazine or other 5-ASA derivatives. If that therapy failed, patients were treated with steroids or even more potent immunosuppressives. Currently, two main therapeutic regimens are being touted, either therapy with a non-absorbable steroid (budesonide) or high dose bismuth preparations. While patients usually respond to the above medications, it is not infrequent for there to be flares of diarrhea after the medication is stopped.

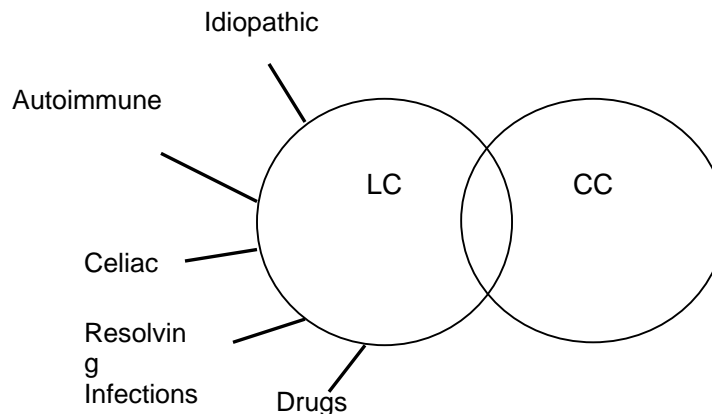
LYMPHOCYTIC COLITIS

Lymphocytic colitis has similar clinical features to collagenous colitis. Watery diarrhea is the main symptom with most individual also noting a mild, intermittent, crampy abdominal pain. Most patients are middle-aged, but in contrast to collagenous colitis, there is an equal male-to-female ratio. Routine hematologic tests are usually normal, but occasionally the Westergren sedimentation is increased. Some patients have increased titers of anti-nuclear antibodies, anti-parietal cell antibodies, and anti-microsomal antibodies. Lymphocytic colitis patients have an increased frequency of HLA A1 and of a diminished frequency of HLA A3 compared to controls.

Pathologic Features: The main histologic feature of lymphocytic colitis is increased intraepithelial lymphocytes. In a normal colon, the number of intraepithelial lymphocytes (IELs) is 5 per 100 epithelial cells, while in lymphocytic colitis, the median number of IELs is 30 lymphocytes per 100 epithelial cells (range 10 to 50). Also, surface epithelial damage and a mild increase in chronic inflammation in the lamina propria is usually seen. There is minimal to no increase in intraepithelial neutrophils, and crypt distortion is generally absent, which sets these cases apart from ulcerative colitis and Crohn's disease. In contrast to collagenous colitis, there is not a subepithelial collagen band – the basement membrane has a sharp, discrete lower border. Also, in comparison to collagenous colitis, there are usually fewer eosinophils, and the amount of chronic inflammation in the lamina propria is usually less.

Pathogenesis: While collagenous colitis is a tightly coherent clinicopathology entity, lymphocytic colitis is more a histologic pattern associated with a variety of conditions. While most of the cases are idiopathic and chronic, some are associated with celiac disease and will resolve when the patients go on a gluten-free diet. A small group of cases is also associated with particular drugs, including ticlopidine, carbamazepine, cimetidine, ranitidine, simvastatin, and some drugs used primarily in France including veinotonics and vinburnine. Finally, cases have been reported following certain infections, and thus may represent a slowly resolving infection or perhaps an abnormal persistent immune response following an infection.

LYMPHOCYTIC COLITIS



MICROSCOPIC COLITIS

Microscopic colitis is a term introduced by Read et al to describe a group of patients with chronic diarrhea that had normal endoscopy, but abnormal histology. Subsequent review of those cases showed them to include collagenous colitis, lymphocytic colitis, eosinophilic colitis, and Crohn's disease. While microscopic colitis is a fine clinical "umbrella" term, pathologists should give a more exacting and specific diagnosis. A microscope is how we make our diagnosis – not a diagnostic entity.

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