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Complications of collagenous colitis

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Abstract

Microscopic forms of colitis have been described, including collagenous colitis. This disorder generally has an apparently benign clinical course. However, a number of gastric and intestinal complications, possibly coincidental, may develop with collagenous colitis. Distinctive inflammatory disorders of the gastric mucosa have been described, including lymphocytic gastritis and collagenous gastritis. Celiac disease and collagenous sprue (or collagenous enteritis) may occur. Colonic ulceration has been associated with use of nonsteroidal anti-inflammatory drugs, while other forms of inflammatory bowel disease, including ulcerative colitis and Crohn's disease, may evolve from collagenous colitis. Submucosal "dissection", colonic fractures or mucosal tears and perforation from air insufflation during colonoscopy may occur and has been hypothesized to be due to compromise of the colonic wall from submucosal collagen deposition. Similar changes may result from increased intraluminal pressure during barium enema contrast studies. Finally, malignant disorders have also been reported, including carcinoma and lymphoproliferative disease.

Key words: Colonic fractures; Colonic perforation; Celiac disease; Collagenous gastritis; Collagenous sprue; Cat scratch colon; Colon cancer; Microscopic colitis

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COLLAGENOUS COLITIS

Collagenous colitis was first described just over 3 decades ago and usually presents as a watery diarrhea syndrome[1]. Distinct histopathologic changes consisting of a colonic mucosal inflammatory process with a characteristic subepithelial hyaline deposit in the lamina propria region (Figures 1 and 2) have been described[1]. These pathological features are analogous to those reported earlier in collagenous sprue[2]. Ultrastructural studies have confirmed that the deposits consist of collagen fibers[3].

Most often, middle-aged to elderly females are affected, although even children have been reported with collagenous colitis[1,4]. The cause has not been defined, but the disorder is very heterogeneous and may have multiple causes. It has frequently been associated with celiac disease[5] and use of a broad range of medications, including nonsteroidal anti-inflammatory drugs and proton pump inhibitors, i.e., lansoprazole[1]. Moreover, there are familial cases suggesting that genetic or heritable factors play a critical role[6]. There are also reports suggesting that collagenous colitis may be precipitated by enteric infections, such as *Yersinia* species or, possibly, bacterial toxins[7-9]. In addition, collagenous colitis has appeared as a reversible paraneoplastic phenomenon[10]. Finally, collagenous colitis has also been recorded in non-human species, such as the baboon[11]. Collagenous colitis may also be readily distinguished from other forms of inflammatory bowel disease (Table 1).

Spontaneous resolution may occur so that evaluation of the response to different therapies may be made more difficult. Even histological endpoints are difficult to evaluate because the sub-epithelial collagen deposits tend to be patchy, rather than diffuse and continuous in mucosal distribution[1]. Treatment has most often focused on symptom resolution using added dietary fiber, non-specific anti-diarrhea agents and anti-inflammatory medications. Steroids, specifically budesonide, were shown to be useful in clinical trials[12]. In some, other immunosuppressants have been used and even surgical treatment has been described[13]. Of note, ileostomy and sigmoidostomy were reported to lead to both clinical and histologic remission. Later ostomy closures, however, led to recurrent symptoms and re-development of collagen deposits. Possibly, a diverted noxious luminal factor was important[14]. Finally, collagenous pouchitis has also been described after restorative proctocolectomy[15].

Long-term studies of collagenous colitis have suggested that it generally runs a very benign clinical course, at least

Table 1 Comparative features of collagenous colitis (CC) with ulcerative colitis (UC) and Crohn's disease (CD)

	CC	UC	CD
Usual age at diagnosis	Mid to older age, most over 40	Youth to middle age	As for UC, most under 40
Sex predominance	Usually female	Similar	Similar
Diarrhea	Watery	Usually bloody	Watery, sometimes with blood
Distribution in colon	Patchy, rare rectal sparing	Continuous with rectal involvement	Patchy or focal; some with rectal sparing
Mucosal involvement	Yes, with	Yes	Yes, with granulomas
Small bowel disease	Occurs; also celiac disease	"So-called 'reflux' ileitis with severe pancolitis"	Common, especially ileum
Complicating cancer	To date, no increased frequency	"Increased rates with extensive disease"	"Increased rates with extensive disease; small bowel cancer"
Autoimmune disorders	Yes	Yes	Yes

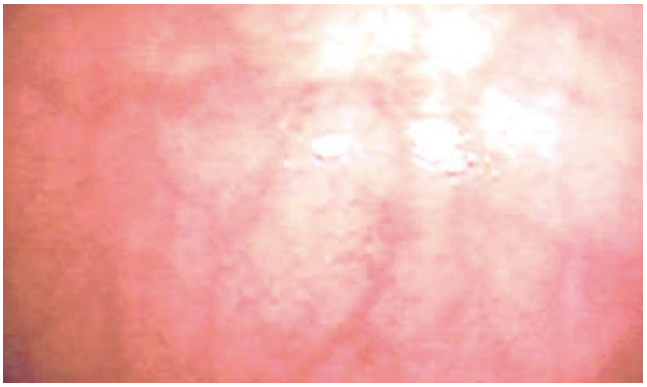

Figure 1 Gross macroscopic appearance of colonic mucosa in collagenous colitis. During colonoscopy, the mucosa may appear virtually normal with minimal alteration in the clarity of the vascular pattern. Diagnosis depends on microscopic evaluation of a colonic biopsy, not the macroscopic appearance of the colonic mucosa.

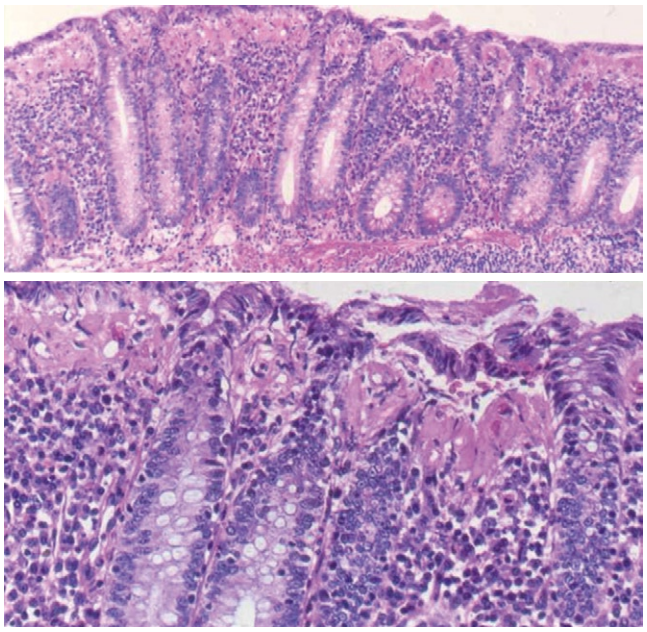

Figure 2 Lower and higher power photomicrographs of the colonic mucosa in collagenous colitis. A mucosal inflammatory process is present with well preserved crypt architecture. Note the subepithelial mucosal band of collagen material.

during evaluation over a period of about 10 years[16]. In most, symptoms spontaneously resolved or remission occurred in association with anti-inflammatory drug therapy alone. Some experienced persistent diarrhea or intermittent periods of recurrent diarrhea that required on-going chronically-administered medication. Occasionally, however, collagenous colitis may be complicated by other disorders of the stomach, small or large intestine and these may dominate its clinical course.

COMPLICATIONS

In a prospective evaluation of established collagenous colitis, celiac disease was subsequently detected in over 20%[5]. This could have implications for patients with celiac disease not appearing to respond to a gluten-free diet; in these, the colonic disease, rather than celiac disease, might be causing symptoms. Collagenous involvement of the gastric and/or small intestinal mucosa also has been detected with collagenous colitis suggesting that, in some, histological changes may not be simply localized in the colon, but may be a far more extensive process[10,17,18]. Even with extensive collagenous involvement of the intestinal tract, however, complete histological remission is possible[10,18].

While most patients with collagenous colitis have a benign or sometimes relapsing and remitting course, recent reports have increased appreciation for some of it's possibly more unusual clinical features involving the colon. A severe and protracted course with a fatal outcome attributed to the colitis has been recorded[19]. Surface epithelial cell sloughing may be appreciated in colonic biopsies leaving a naked subepithelial deposit; in many of these patients, mucosal permeability may be altered and protein-losing enteropathy has been noted in the absence of small intestinal disease[20]. Colonic ulceration may occur, possibly related to concomitant use of medications, such as nonsteroidal anti-inflammatory drugs[21]. Occasionally, evolution of collagenous colitis into severe ulcerative colitis or Crohn's disease has been recorded[22-24]. With the onset of ulcerative colitis, complete disappearance of the collagen deposition occurred[22]. Rarely, submucosal "dissection" may occur[25]. Colonic fracturing after endoscopic instrumentation, possibly related to air insufflation and barotrauma, or insertion of barium contrast agents, has been recorded[26]. Recently, a report entitled "cat scratch colon" emphasized the macroscopic changes involving the proximal colon that are most often observed during colonoscopy in collagenous colitis[27]. Spontaneous peritonitis with colonic perforation has also been recorded[28]. In all of these, it has been hypothesized that the integrity of the colonic wall may be compromised owing to submucosal collagen deposition.

A particularly striking finding, to date, is the rarity of reported malignant disease complicating the clinical course of collagenous colitis. Colorectal cancer has been noted[10,29], including cecal cancer[30], but these may have been only coincidental. In an extensive survey study, the overall risk of colorectal cancer was similar to the general control population; only 2 patients with collagenous colitis were seen with colorectal cancer, but these occurred before development of colitis[31]. Interestingly, collagenous involvement of the small and large intestine resolved completely following resection of a colon cancer suggesting an unusual paraneoplastic phenomenon[10]. Other neoplasms that have been rarely recorded include lymphoproliferative disorders[32,33] and carcinoids[34]. Because this is a relatively "new" disease, sufficient time may not yet have passed to observe sufficient superimposed disease complications. Alternatively, factors linked to pathogenesis, such as the use of nonsteroidal anti-inflammatory drugs, may induce a chemopreventive effect on development of colonic neoplasia.

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