Pseudomembranous Collagenous Colitis

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Abstract: The classic clinical and histologic features of collagenous colitis are well characterized; however, the acute or neutrophilic inflammatory changes that may accompany this entity are less well established. In this report of 10 patients, we describe the first series of pseudomembranous collagenous colitis. Because superimposed *Clostridium difficile* infection was only demonstrated in one patient and no other causes of pseudomembranous colitis were evident in the remaining nine patients, we conclude that pseudomembranes are part of the spectrum of collagenous colitis itself. This case series illustrates the importance of searching for collagenous colitis in the evaluation of pseudomembranous colitis. At the same time, superimposed infectious or ischemic etiologies need to be excluded clinically in any patient with superimposed pseudomembranes. The existence of pseudomembranes in collagenous colitis also lends support to the hypothesis that toxin- and/or ischemia-mediated injury may be involved in the pathogenesis of collagenous colitis.

Key Words: collagenous colitis, pseudomembranous colitis

Dedication: We dedicate this work to the memory of our irreplaceable colleague, the late Dr. Rodger C. Haggitt, whose keen skills of observation and critical thinking made this work possible.

(*Am J Surg Pathol* 2003;27:1375–1379)

Collagenous colitis was first described by Clas Lindström in 1976.[13] His original classic case report describes a 48-year-old woman with chronic watery diarrhea, normal endoscopic findings, and a remarkable deposition of subepithelial collagen in a rectal biopsy. Since then, more than 500 cases have been reported, and these originally described features, among others, have become fully established.[4,16]

Given the lack of endoscopic or other findings in the majority of these patients, the diagnosis of collagenous colitis rests upon the histopathology of affected colorectal mucosa. While the abnormalities of the collagen table, intraepithelial lymphocytosis, luminal epithelial sloughing, lamina propria expansion, and maintenance of crypt architecture are all well described in the literature,[16] the spectrum of active or acute inflammation that may be seen in collagenous colitis has not received much attention. Scattered intraepithelial neutrophils are not uncommon, and crypt abscesses have been more recently reported[2]; however, reports of fibrinopurulent surface pseudomembranes are rare and anecdotal. This case series more fully examines pseudomembranous change in collagenous colitis.

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MATERIALS AND METHODS

Clinical

University of Washington Human Subjects Division approval was provided for this study. Ten patients with collagenous colitis and pseudomembrane formation were identified from the surgical pathology files, or the gastrointestinal pathology consultative files at the University of Washington, during the period of 1994 to 2003. Routinely processed, hematoxylin and eosin-stained slides were examined. Trichrome-stained slides, where available, were also reviewed. At least two endoscopic biopsies and an average of seven were evaluated from each of 10 patients. Clinical information was collected regarding gender, age, symptoms, endoscopic findings, clinical evidence for possible ischemia, results of stool cultures, and toxin assays, particularly those for *Clostridium difficile* and *Escherichia coli O157:H7*, drug use (particularly nonsteroidal anti-inflammatory drug [NSAID] and estrogen use), and finally outcome data.

Histology

To establish the histologic diagnosis of collagenous colitis, the following criteria were required: preserved crypt architecture and a morphologically abnormal subepithelial collagen table (Figs. 1–3). The collagen table criteria included irregular thickening with an often spiculated interface with the subjacent lamina propria and incorporation of inflammatory cells, fibroblasts, and capillaries. The thickness of the collagen table was measured for presentation of data, but formal measurements were not performed for practical clinical diagnostic purposes. The collagen table morphologic features were considered more specific and sufficient. Typically present features that were not absolutely required for the diagnosis but were analyzed included intraepithelial inflammatory cells and crypt abscesses, inflammatory cell expansion of the lamina propria content, often exhibiting a "top-heavy" distribution (denser

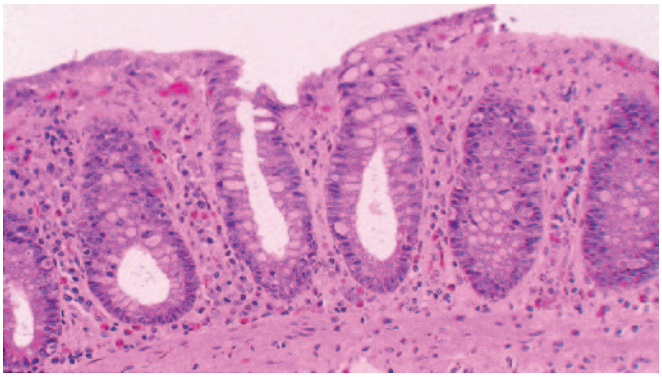

FIGURE 1. Collagenous colitis demonstrating preserved crypt architecture, expansion of the lamina propria, and a markedly abnormal subepithelial collagen table showing irregular thickness, a spiculated interface with subjacent lamina propria, and incorporation of capillaries, red cells, fibroblast, and inflammatory cells into the collagen. Note also the surface colonocyte damage and partial denudation (hematoxylin and eosin, original magnification ×200).

collections in the upper or luminal aspect of the lamina propria), intraepithelial lymphocytosis (>20 per 100 epithelial cells, although this was not directly quantitated but rather was estimated), and surface colonocyte damage with or without luminal sloughing.

RESULTS

Clinical

All of the patients were women with a mean age at diagnosis of 59 years (range, 31–81 years), and all presented with chronic watery diarrhea (Table 1). Information was available on five patients that excluded an infectious etiology. Only one patient had a positive *C. difficile* toxin assay. Ischemia was excluded in all patients based on clinical evaluation and histologic features of evaluated biopsies. Specifically, none of the patients had a known cardiovascular or hypotensive event or history of cardiovascular disease, and none of the colonoscopic biopsies showed features of acute or chronic ischemia other than pseudomembranes. In one patient, ischemia was also excluded with a negative flow MRI study. Clinicopathologic features of idiopathic inflammatory bowel disease were also absent in all patients. NSAID or estrogen use was excluded in four patients and identified in two. One patient had been taking Advil until 1 month prior to the onset of her symptom. Another patient had a history of long-term use of both Sulindac and estrogen. The medication histories on the remaining four patients were not available.

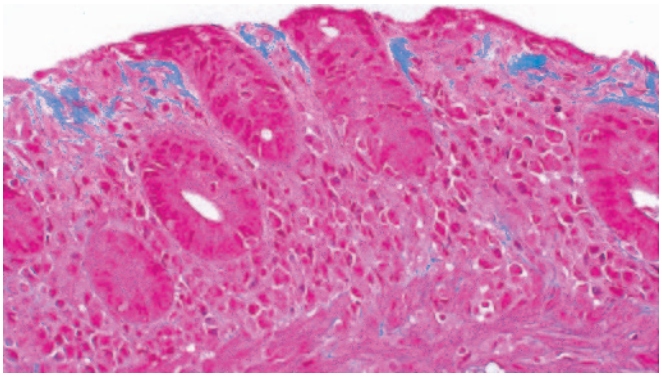

FIGURE 2. This trichrome stain and higher power magnification accentuate the irregular and spiculated nature of the subepithelial collagen table (Masson's trichrome, original magnification ×400).

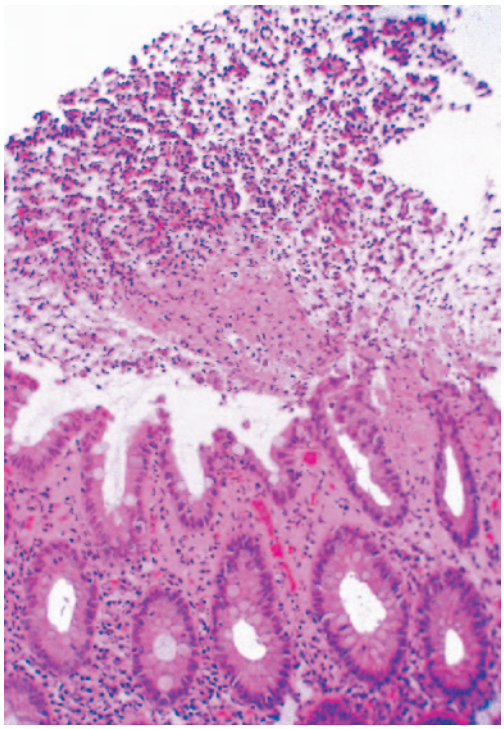

FIGURE 3. A fibrinopurulent pseudomembrane erupts from the surface of a colonic biopsy with pseudomembranous collagenous colitis (hematoxylin and eosin, original magnification ×100).

Histology

A total of 72 endoscopic colonic biopsies from 10 patients were reviewed. Seventeen colonic biopsies showed no histologic evidence of collagenous colitis or other pathology, a not uncommon finding in patients with the disorder, demonstrating its often-patchy distribution. These normal biopsies were excluded from further evaluation. A total of 55 pathologic colonic biopsies were analyzed and these were derived from the following sites: cecum (4), ascending colon (12), hepatic flexure (1), transverse colon (6), descending colon (12), sigmoid (3), rectum (2), and undesignated (15).

TABLE 1. Pseudomembranous Collagenous Colitis: Clinical Characteristics

Patient No.	Age (yr) (at Diagnosis)/Gender	Duration of Diarrhea	Endoscopic Findings	Endoscopic Diagnosis	*C. dificile/E. coli* O157:H7	Ischemia	Estrogen/ NSAID Use
1*	31/F	Unknown	NA	Proctitis/ASLC	+/ND	Excluded	No/No
2	67/F	Chronic	TC linear ulcers	Crohn's	ND/ND	Excluded	NA
3*†	56/F	7 weeks	Normal	NA	−/−	Excluded	No/No
4	67/F	6 weeks	Ulcers in TI and RC	Crohn's	ND/ND	Excluded	NA
5*†	64/F	8 weeks	Inflamed rectum	Ulcerative colitis	−/ND	Excluded	No/No
6†	54/F	Unknown	TI and cecum ulcers	Crohn's	−/ND	Excluded	No/Yes
7	67/F	6 years	NA	NA	NA/NA	Excluded	NA
8	49/F	Months	RC ulcers	NA	ND/ND	Excluded	NA
9*†	61/F	8 weeks	Erythema and granularity	Crohn's	−/−	Excluded	Yes/Yes
10†	81/F	2 weeks	RC ulcer and erythema	Crohn's	−/−	Excluded	No/No

NA, not available; TC, transverse colon; TI, terminal ileum; RC, right colon; ND, not done; ASLC, acute self-limited colitis.
*No pathogenic organisms identified in stool culture.
†Stool examination negative for ova and parasites.

Pseudomembranes consisted of neutrophils, necrotic debris, fibrin, and occasionally, detached epithelium (Fig. 3). Pseudomembranes were seen in 52.7% (29 of 55) of the biopsies with the following distribution: cecum (3), ascending colon (4), hepatic flexure (1), transverse colon (3), descending colon (3), sigmoid (2), rectum (2), and unspecified (11).

None of the following changes of acute or chronic ischemia was present: superficial zonal acute necrosis of epithelium and stroma, chronic atrophy of crypts, full-thickness lamina propria fibrosis, crypt architectural distortion, or hemosiderin deposition.

The surface mucosa frequently showed evidence of epithelial damage, where flattening, detachment, and /or denudation, pseudostratification, and regenerative epithelial changes could be seen (Figs. 1, 2). These areas also showed varying degrees of intraepithelial neutrophilic and/or eosinophilic inflammation and intraepithelial lymphocytosis of the surface and crypt epithelia (Table 2). There was no evidence of ulceration or erosion, and only one crypt in one biopsy (1.8%) showed a crypt abscess, which was in intimate association with pseudomembrane formation in that biopsy.

The subepithelial collagen layer thickness exceeded 10 μm in all cases (mean, 44.3 μm; range 13.4–100 μm) and showed no correlation with the presence or absence of pseudomembrane formation. Thickness varied throughout the colon. Further, pseudomembranes were consistently associated with mucosa also showing features of collagenous colitis in all cases.

The subepithelial collagen layer had a variegated appearance within individual biopsy specimens, and its morphology was considered more pertinent to the diagnosis of collagenous colitis than its absolute thickness. Some areas revealed a normal collagen table with a homogenous, thin, and smoothly undulating border. However, more of the biopsies demonstrated an irregular appearance to the collagen table with a jagged border at the interface with the subjacent lamina propria (Figs. 1–3); occasionally, both patterns were present in one patient or even one biopsy. Incorporation of fibroblast nuclei was seen uniformly in all affected biopsy specimens. Small capillaries and trapped red blood cells within the subepithelial collagen table were present in 96.4% (53 of 55) of the affected biopsy specimens. Also seen within the collagen table were a variety of inflammatory cells, including neutrophils, eosinophils, plasma cells, and lymphocytes.

Crypt architecture was preserved in all patients, as is highly characteristic of collagenous colitis. Expansion of the lamina propria by prominent lymphocytic, plasmacellular, eosinophilic, and neutrophilic inflammation was common. Intra-

TABLE 2. Mucosal Histology in Pseudomembranous Collagenous Colitis (55 Total Involved Biopsies)

	Surface Intraepithelial	Crypt Intraepithelial	Expansion of Lamina Propria*
Neutrophils	9 (16.4%)	23 (41.8%)	33 (60.0%)
Lymphocytes	28 (50.9%)	34 (61.8%)	55 (100%)
Eosinophils	16 (29.1%)	7 (12.7%)	49 (89.1%)
Pseudomembranes	29 (52.7%)		

*Lamina propria expansion refers to a visual estimate of the increase in the overall cellularity of the lamina propria inflammatory cell content, relative to normal content for each given location in the colon, noting that right colon is normally more cellular and left colon. These data indicate the number of biopsies and percentage of the total number of involved biopsies with relatively increased lamina propria neutrophils, and/or lymphocytes, and/or eosinophils.

epithelial inflammatory cells consisted predominantly of lymphocytes, but eosinophils and neutrophils were also observed. Some variation in the surface versus crypt distribution of intraepithelial inflammatory cells was noted (Table 2).

Endoscopic diagnoses were available in seven patients and are listed in Table 1. The endoscopic impressions in these patients were Crohn's disease (5), ulcerative colitis (1), and proctitis versus acute self-limited colitis (1). Three biopsies were taken from ulcer sites. However, changes of ulceration were not present in these biopsies, which on the whole appeared similar to biopsies taken from other sites with pseudomembranes and mild focal active inflammation. Due to the lack of specific site designation for most of the biopsies, further endoscopic-histologic correlation was not possible.

We obtained clinical outcome data on seven patients. Six were treated with various combinations of anti-inflammatory agents such as mesalamine (Asacol, Pentasa), cortisol enema, and antidiarrheal medications such as loperamide (Imodium). Five patients responded well to treatment. Among them, we know of one patient who experienced a recurrent episode of less severity about 5 years later. Another patient with only limited follow-up due to recent presentation in February 2003 still had persistent symptoms 1 month after treatment at her most recent follow-up visit. The seventh patient experienced three recurrent episodes in the 10 years since her initial presentation. She initially responded well to beclomethasone after failing conventional anti-inflammatory agents but required 6-mercaptopurine for the last two episodes. She was in remission at the most recent follow-up. Overall, the clinical outcome of these patients is similar to that of patients with typical collagenous colitis without pseudomembrane formation.

DISCUSSION

The classic clinical and histologic features of collagenous colitis have been well characterized. However, the spectrum of acute inflammatory change occurring in this disorder has received little attention. In particular, pseudomembranous change in collagenous colitis is the subject of rare anecdotal case reports only. This case series of 10 patients more fully documents pseudomembranous collagenous colitis as part of the spectrum of this disorder.

A recent case series of collagenous colitis revealed active crypt inflammation in 30% of patients and ulceration in 2.5%.[2] These findings indicate that active inflammation is not uncommon in collagenous colitis and that it should not preclude the diagnosis of collagenous colitis. Pseudomembranous change can now be included within the evolving concept of the spectrum of acute inflammatory changes that occur in collagenous colitis.

Pseudomembranous colitis is an injury pattern and not a specific diagnosis. The differential diagnosis for pseudomembranous colitis principally includes toxin-induced, infectious, or ischemic etiologies. Infectious or toxic injury to colonocytes is epitomized by the familiar *C. difficile* pseudomembranous colitis.[7] Toxin-induced infectious pseudomembranous colitis may also be caused by enterotoxigenic *E. coli*, most notably the *E. coli O157:H7* serotype.[18] These toxins may actually work through an ischemic mechanism by producing vasoconstriction. Ischemic colitis produced by colonic vascular hypoperfusion of many causes may also produce a pseudomembranous pattern of inflammation.[7]

Pseudomembranous collagenous colitis is uncommon, relative to infectious or ischemic pseudomembranous colitides. Review of the literature reveals only four other individual patient reports of collagenous colitis with pseudomembranes.[3,10,17] Treanor et al presented a single case of a 56-year-old woman with a history of exacerbation of intermittent diarrhea over many years.[17] Random colonic mucosal biopsies showed striking pseudomembranes. *C. difficile* toxin was not identified in the stool samples at the time. Giardiello et al reported two cases of elderly white male patients with collagenous colitis associated with pseudomembranes.[10] Neither patient had evidence of *C. difficile* toxin or infection, and both showed improvement with anti-inflammatory agents after the diagnosis of collagenous colitis was made. A study from Spain reported one patient with aphthous ulcers and pseudomembranes.[3]

The present retrospective series of 10 patients with pseudomembranous collagenous colitis further substantiates this association and variant forms of collagenous colitis. Because no other cause of pseudomembranous colitis was identified in nine of 10 patients, we conclude that pseudomembranes appear to be part of the spectrum of collagenous colitis itself.

As illustrated by this series and the above case reports, it is important to search for the features of collagenous colitis in the evaluation of any pseudomembranous colitis. However, because of the apparent rarity of pseudomembranous collagenous colitis, superimposed infectious or ischemic etiologies need to be excluded in any patient with both features. Appropriate stool cultures and toxin assays, particularly for *C. difficile* and *E. coli O157:H7* and investigation into possible ischemic etiologies are essential for the correct diagnosis. Of note regarding this issue, one of the 10 patients in this series of collagenous colitis with pseudomembranes had a concurrent positive *C. difficile* toxin assay. On repeat biopsies, after antibiotic treatment, the pseudomembranes and even the features of collagenous colitis had apparently resolved. In another report of a similar case, pseudomembranes disappeared on repeat biopsies 4 months later after metronidazole treatment, but the subepithelial collagen layer thickening persisted.[19] Khan et al also reported a case of collagenous colitis developing after recurrent *C. difficile* infection of the colon and pseudomembranous colitis.[12] Thus, while collagenous colitis alone, without other identifiable etiologies, may produce pseudomembranous colitis, infection and ischemia are more common causes

of pseudomembranous colitis and should be excluded as potentially superimposed pathologies in collagenous colitis patients.

The use of various medications has been associated with colitis, some of which might act through an ischemic mechanism that could result in the formation of pseudomembranes. The gastrointestinal toxicity of NSAIDs has long been recognized.[9,15] Of note, NSAIDs have also been speculated to play a role in pseudomembranous and in collagenous colitis.[10] More recently, estrogen use has also been implicated in the development of ischemic colitis.[6,8,14] It is possible that in two of our patients, the use estrogen and NSAIDs contributed to the development of pseudomembranes in the setting of collagenous colitis, although the extent of the contribution is unknown.

Overall, the clinical outcome of these patients in this retrospective series is similar to that of patients with typical collagenous colitis without pseudomembrane formation. Most respond well to conventional anti-inflammatory and antidiarrheal agents with a few episodes of recurrence. However, in one case, beclomethasone and eventually 6-mercaptopurine were required to achieve remission.

The observation of pseudomembrane formation in collagenous colitis may also shed light on the elusive etiology of this disease. Specifically, the presence of associated pseudomembranes supports the hypothesis that collagenous colitis may be caused by a toxic and/or ischemic mechanism, given the prevalence of pseudomembranous colitis in these two settings classically in the absence of collagenous colitis. There is independent evidence supporting an exogenous toxin-induced process in collagenous colitis. Diversion of the fecal stream has been shown to induce both histopathologic and clinical remission of collagenous colitis in some patients,[11] possibly due to the decreased concentration of fecal toxins. The effect of antibiotics and the sudden onset of the disease in some patients may point to a microbiologic source of toxins in those cases.[5] An interesting case reported by Andersen et al showed that following metronidazole and cholestyramine therapy, a patient with collagenous colitis showed improvement in symptoms, disappearance of histologic changes, as well as reduced fecal cytotoxicity on McCoy cell lines.[1] The authors hypothesized that an unidentified bacterial cytotoxin might be involved in the pathogenesis.

In summary, we have reported a series of 10 patients with pseudomembranous collagenous colitis. No other cause was identified in nine of these patients, so we conclude that pseudomembranous change is part of the pathologic spectrum of collagenous colitis itself. Superimposed *C. difficile* colitis was identified in only one of the 10 patients in our series, and this indicates the need to assess for concurrent and statistically far more common infectious and ischemic pathologies whenever pseudomembranes are found in association with collagenous colitis. Further, pseudomembrane formation in collagenous colitis adds support to toxic and/or ischemic theories of the pathogenesis of collagenous colitis. Collagenous colitis may now be added to the list of differential diagnoses for patients with pseudomembranous colitis.

ACKNOWLEDGMENTS

The authors thank the clinicians caring for these patients who provided the additional clinical data that made this study possible. They include, Drs. Sol Barnett, Carl Dettwiler, Robert Etlinger, John W. Hoyt, James Kruidenier, Barry Levenson, Douglas Levine, Catherine Little, D. B. Michaels, James Rosenberg, Ned Snyder, and Kenneth A. Vogele. We also wish to thank Ms. Judy Renando for her excellent secretarial support.

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