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Sequential Histologic Evaluations in Collagenous Colitis

Correlations with Disease Behavior and Sampling Strategy

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To evaluate the histologic manifestations of collagenous colitis and correlate histologic changes with disease behavior, 14 patients who had undergone sequential evaluations during 33 ± 6 months of follow-up were studied. Two hundred twelve tissue specimens from all anatomic regions of the colon (mean, 15 ± 3 samples per patient) were interpretated independently under code by two pathologists. Eight patients (57%) had histologic resolution after 14 ± 4 months of empiric therapy and in only one of these (12%) did symptoms persist. Four patients (29%) had sequential histologic examinations from the same anatomic region that varied from classical collagenous colitis to inflamed mucosa without a thickened collagen band to normal mucosa. Eight patients (57%) had varying histologic findings from different anatomic regions during the same examination that ranged from classical collagenous colitis to increased inflammation with resolution of the collagen band to normal mucosa. Normal mucosa was found mainly in specimens from the rectosigmoid, and proctosigmoidoscopic examinations alone would have missed the diagnosis of collagenous colitis in 40% of cases. Pathologic interpretations were concordant in 171 of 212 instances (81%). We conclude that histologic resolution of collagenous colitis can occur and it is associated with loss of symptoms. The histologic features of collagenous colitis are distinctive, but they may be patchy and inconsistently sampled. Rectosigmoid biopsies underestimate the diagnosis.

KEY WORDS: microscopic colitis; lymphocytic colitis; collagenous colitis.

Collagenous colitis is now recognized as a distinct pathologic entity that may be found in patients with watery diarrhea and normal or near-normal colonoscopic examinations (1–3). Its diagnostic feature is a bandlike deposition of collagen beneath the surface epithelium, around the absorptive capillary complex, and between the myofibroblasts in the upper lamina propria of the colonic mucosa (2, 4–6). Mild mixed but predominantly mononuclear infiltrates are present in the lamina propria and a characteristic feature is the presence of increased numbers of intraepithelial lymphocytes in surface and crypt epithelium (2).

The etiology of collagenous colitis remains unknown, but its association with celiac disease (7–9),

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chronic hepatitis (2), inflammatory arthropathies (1, 10–13), type A atrophic gastritis (14), diabetes (1, 2, 5) and autoimmune thyroid disease (1, 5, 6, 14) suggests an immunologic mechanism that may be triggered by foods, drugs, toxins, infection, or environmental factors (2, 15, 16). No specific therapy has been shown to be effective (1, 17), but remissions of the disease have been described, including disappearance of the collagen band (2, 5, 18–20). Unfortunately, the frequency of such an occurrence is unknown, and it is still unclear if clinical remission correlates closely with histologic resolution, if histologic resolution is a manifestation of mucosal sampling error or a true end point of the disease, and if relapse connotes reappearance of the disease or incomplete resolution of the original process.

Recently, microscopic ("lymphocytic") colitis, which has the same histologic features as collagenous colitis except for the absence of a subepithelial collagen layer (21, 22), has been proposed as being either part of the spectrum of collagenous colitis (23) or a separate but related entity (24). The histologic similarities between the disorders (21, 22) and the recognition of the features of each entity at the same or different times in the same patient (16, 23) have supported the former hypothesis, while the apparent infrequency of spontaneous transitions between the disorders and differences in sex ratios and HLA phenotypes have supported the latter contention (21). Unfortunately, sequential evaluations in a well-defined patient population have not been performed to resolve the issue.

In this study, we assess histologic resolution of collagenous colitis in symptomatic patients who have undergone serial clinical, endoscopic, and histologic evaluations, and we correlate histologic changes with clinical features. We determine the concordance of two pathologists in the interpretation of the histologic findings and we assess mucosal sampling variability in diagnosing the condition.

MATERIALS AND METHODS

Study Population. Fourteen patients with watery diarrhea; normal, or near-normal colon examinations by contrast study or endoscopy; and mucosal biopsy evidence of collagenous colitis, comprise our study population. Twelve of the 14 patients (86%) were women. Ages ranged from 39 to 73 years (mean 58 ± 3 years) and diarrheal symptoms had been present for two months to 40 years (mean 62 ± 35 months). The patient with 40 years of diarrhea had been evaluated on multiple occasions prior to her Mayo assessment, and no specific cause for her symptoms had been identified. Unfortunately, mucosal biopsies of the colon had not been obtained earlier, and it was not possible to determine if her diarrhea had been originally or always due to collagenous colitis.

Each patient had been assessed on at least two occasions (mean number of clinical evaluations 5 ± 1; range 2–10) during 33 ± 6 months of follow-up (range 3–82 months). By requirement, each had undergone at least one colonoscopic examination with universal mucosal sampling at presentation or during follow-up (mean number of colonoscopic examinations, 2 ± 0.5; range 1–7). Flexible 60-cm proctosigmoidoscopy had also been performed in 12 of the patients (range 1–8 examinations; mean 4 ± 1) and mucosal samples had been obtained from the rectum, sigmoid, and distal descending colon. The anatomic location from which each biopsy was obtained was recorded and findings from different locations in the same patient were compared as well as findings from the same location at different times in the same patient. All patients had received empiric drug therapy administered at the discretion of their primary physician (Table 1).

Clinical Assessment. Complete clinical histories had been obtained at each follow-up visit and physical examinations and conventional laboratory tests had been performed (1). The clinical findings were subsequently reviewed by one of the investigators (W.J.T.), who classified the clinical disease as being active (diarrheal symptoms unchanged or worse), improved (diarrheal symptoms better but still present), or in remission (diarrheal symptoms fully resolved). A return of diarrheal symptoms after clinical remission connoted clinical relapse.

Histologic Assessment. Two hundred twelve tissue specimens had been obtained from throughout the colon in the 14 patients during the course of follow-up (mean number of specimens from each patient 15 ± 3; range 3–47). Ninety-seven specimens (46%) had been obtained from the rectosigmoid and 115 samples (54%) had been obtained from all regions of the colon from the cecum through the descending portion. From each of the 212 tissue samples, three glass slides were prepared and on each, multiple 6- to 8-μm-thick tissue sections were mounted and stained with hematoxylin and eosin. A single glass slide was selected at random from these three and included in the final study set. The 212 slides in the study set were then randomly arranged and each slide was interpreted under code independently by the two pathologists (H.A.C. and K.P.B.). The histologic findings were classified in accordance with predefined criteria (2, 5, 21, 22, 25). The number of intraepithelial lymphocytes was estimated as a mild, moderate, or marked increase above normal. The independent histologic diagnoses were compared, and the degree of concordance between the pathologists was determined.

Discrepancies in histologic interpretation were subsequently resolved by having both pathologists simultaneously review each tissue sample in question through a two-headed microscope, discuss the features, and agree on a single diagnosis. Tissue samples were then reorganized into sets by patient name, biopsy date, and biopsy site. Variations in the histologic findings in different regions of the colon were then analyzed and changes in

TABLE 1. TREATMENTS AND OUTCOMES OF COLLAGENOUS COLITIS

Patients	*Treatments**	*Histologic resolution*	*Clinical remission*	*Histologic relapse†*	*Clinical relapse†*
1	5-ASA	+	+	−	−
2	5-ASA	+	+	−	−
3	5-ASA and prednisone	+	+	+	+
4	5-ASA and prednisone	+	+	+	−
5	SAS	+	+	NO F/U	NO F/U
6	SAS and prednisone	+	+	NO F/U	NO F/U
7	Prednisone	+	+	NO F/U	NO F/U
8	5-ASA and prednisone	+	−	+	−
9	SAS and prednisone	−	+	−	+
10	SAS	ND	+	NO F/U	NO F/U
11	5-ASA and prednisone	−	−	−	−
12	SAS and prednisone	−	−	−	−
13	SAS and prednisone	−	−	−	−
14	SAS and others	−	−	−	−

*5-ASA = oral 5-aminosalicylic acid; SAS = sulfasalazine; others = corticosteroid enemas, clonidine, chlorpromazine.
†ND = biopsy not done; NO F/U = no follow-up.

the histologic findings in the same anatomic site were determined. The histologic features were correlated with the clinical assessment at the time of biopsy.

Criteria for Histologic Diagnoses. Histologic diagnoses were rendered separately on individual biopsy specimens rather than evaluating the entire case as a whole. The diagnosis of collagenous colitis required the presence of a subepithelial collagen layer that could be patchy, dense, or delicate but necessarily was distributed around the capillaries and between the myofibroblasts in the upper lamina propria, obscuring the lower border of the surface epithelial basement membrane (2, 4, 5, 25). Also required was evidence of a nondestructive chronic inflammatory process characterized by a mixed, predominantly mononuclear, inflammatory cell infiltrate in the lamina propria and increased crypt mitoses. The mixed inflammatory infiltrate included at least some neutrophils in addition to mononuclear cells and eosinophils. An increase in the numbers of intraepithelial lymphocytes, neutrophils, and eosinophils as well as findings of surface epithelial cell damage and sloughing were not required for the diagnosis, but they could be present (2, 4, 5, 25). Since reported values for the thickness of the collagen layer have varied (1–3, 6, 25, 26) and the specificity of the finding has been questioned (27, 28), our definition of collagenous colitis was based on the location and distribution of the collagen rather than a measured thickness (2, 25).

The presence of a mixed, predominantly mononuclear, cell infiltrate in the lamina propria comprised of mononuclear cells, at least rare neutrophils, and a variable number of eosinophils in the absence of a subepithelial collagen layer is the histologic picture of microscopic colitis (21, 22). In the assessment of individual biopsy specimens, therefore, the presence of such findings justified this histologic classification independent of the clinical diagnosis of collagenous colitis. Other features of this histologic diagnosis were increased crypt mitoses and absence of crypt architectural distortion. Increased numbers of intraepithelial lymphocytes, some degree of surface epithelial damage and/or sloughing, and neutrophils or eosinophils within the epithelium could be variably present (21, 22, 29).

The absence of all pathologic features or the presence of mild nonspecific ("reactive") changes justified the histologic diagnosis of normal mucosa. Mucosal specimens could have a slight increase in the number of mononuclear cells in the upper lamina propria and an increase in the number of crypt mitoses but no evidence of an established inflammatory process as characterized by the presence of neutrophils.

Statistical Analysis. Chi-square analysis with Yates' correction was used to compare dichotomous variables. Data are presented as the mean ± SEM in tables and text.

RESULTS

Histologic Resolution and Clinical Findings. Eight of the 14 patients (57%) had normal histologic examinations after 14 ± 4 months (range 3–37 months) of empiric therapy with antiinflammatory medication (Table 1). Seven of these (88%) had a corresponding clinical remission. The histologic findings correlated with the clinical findings in 11 of the 14 patients (79%). Only one patient (patient 8, Table 1) had persistent diarrhea without histologic abnormalities, and this individual subsequently had histologic evidence of recurrent disease five months later. Another patient (patient 9, Table 1) had resolution of diarrheal symptoms with persistent histologic features of collagenous colitis, and she developed recurrent diarrhea 17 months later. Unfortunately, one patient (patient 10, Table 1) did not have mucosal sampling at the time of clinical remission and the status of his disease was indeterminate. Disappearance of symptoms occurred mainly in those who had reverted to normal histologic fea-

tures (seven of eight patients with normal mucosa versus one of five patients with documented abnormal mucosa).

Four of the seven patients who achieved histologic resolution and clinical remission were subsequently followed for 19 ± 3 months (range 13–27 months) (patients 1, 2, 3, and 4; Table 1), and two had histologic recurrence of collagenous colitis after 21 and 27 months of observation (patients 3 and 4, Table 1). Clinical relapse, however, occurred in only one of these patients. The two patients who continued to have normal histologic findings (patients 1 and 2, Table 1) had no diarrheal symptoms during 13 and 14 months of observation after discontinuation of 5-ASA.

Histologic resolution occurred more commonly in patients receiving regimens containing oral 5-ASA (83%) than in those receiving sulfasalazine (29%) or prednisone (55%) (Table 1), but the differences were not statistically significant. Interestingly, only the two patients receiving 5-ASA alone achieved a sustained clinical remission and histologic resolution.

Variations in Histologic Findings from Same Anatomic Region. Sequential histologic examinations from the same anatomic site showed features of classical collagenous colitis, increased mucosal inflammation but absence of a collagen band, and normal mucosa at different times in four of the 14 patients (patients 2, 4, 8, and 10; Table 1). On the biopsy specimens with inflammation but no collagen band, the clinical diagnosis of microscopic colitis would have been justified if these samples had been seen in isolation. In an additional four patients (patients 1, 3, 6, and 7; Table 1), histologic features of collagenous colitis and normal mucosa were found in the same anatomic region at different times.

Variations in Histologic Findings from Different Anatomic Regions. In eight patients, histologic features of collagenous colitis, increased mucosal inflammation in the absence of a collagen band, and normal mucosa were demonstrated in different anatomic sites during the same endoscopic examination. In two of these patients, features of collagenous colitis, increased mucosal inflammation without a collagen band, and normal mucosa were seen; in two others, features of collagenous colitis and normal mucosa were seen; and in four others, features of collagenous colitis and mucosal inflammation without a collagen band were seen. In the instances of mucosal inflammation without a collagen band, the clinical diagnosis of microscopic colitis would have been justified if the specimens had been evaluated in isolation.

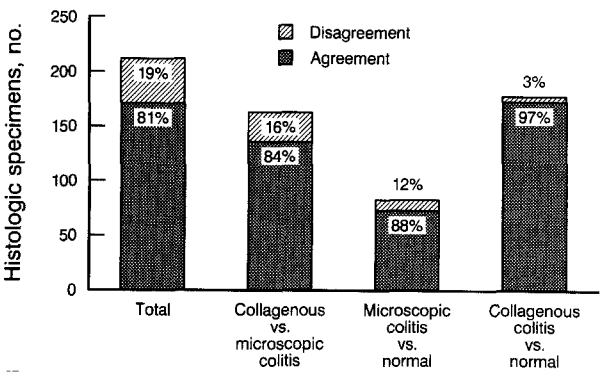

Fig 1. Concordance of the two pathologists in the interpretation of the histologic findings. The frequencies of agreement and disagreement are shown by percentages within each bar for the total experience and for each of the histologic distinctions.

Normal mucosa was found only in the rectosigmoid. Features compatible with the histologic diagnosis of microscopic colitis were demonstrated in the right colon proximal to features of classical collagenous colitis during six endoscopic examinations; in the left colon distal to features of collagenous colitis during four endoscopic examinations; and proximal as well as distal to features of collagenous colitis in the transverse colon during three endoscopic examinations. Proctosigmoidoscopic examinations would have missed the diagnosis of collagenous colitis in 12 of 30 instances (40%) in which the diagnosis was evident in simultaneously obtained tissue samples from regions in the proximal colon.

Concordance of Histologic Interpretations. When the two independent histologic interpretations were compared sample by sample, there was complete agreement in 171 of 212 instances (81%). Of the 41 discrepant interpretations, 27 were disagreements between the histologic diagnoses of collagenous colitis and microscopic colitis; 10 were disagreements between the histologic diagnoses of microscopic colitis and normal mucosa; and five were disagreements between the histologic diagnoses of collagenous colitis and normal mucosa. Importantly, of 163 mucosal samples interpreted as collagenous colitis or microscopic colitis, there were discrepancies in only 27 instances (Figure 1). Of 83 tissue samples interpretated as microscopic colitis or normal mucosa, there were discrepancies in only 10 instances (Figure 1) and, of 178 tissue samples interpreted as collagenous colitis or normal mu-

cosa, there were discrepancies in only five instances (Figure 1). Discrepant interpretations were attributed mainly to the subtlety of the changes, small sample size, and artifact. The histologic diagnoses did not alter the clinical diagnosis of collagenous colitis in any of our patients.

DISCUSSION

Our study indicates that histologic resolution occurs commonly in symptomatic patients with collagenous colitis who are treated empirically with antiinflammatory medications. Histologic abnormalities resolved in 57% of patients and, most importantly, reversion of the colonic mucosa to normal was associated with clinical remission in seven of eight patients. Histologic findings typically correlated with clinical findings but discrepant clinical and histologic findings did occur in two of our patients. In one of these, clinical remission eventuated despite persistence of histologic disease, and in another, diarrhea continued despite resolution of histologic abnormalities. In the patient who achieved clinical remission, diarrheal symptoms recurred. Although asymptomatic, histologically documented, collagenous colitis is possible (16), such a condition has not been described commonly, and in our patient the persistence of histologic abnormalities in the absence of symptoms may have been an early indication of her subsequent clinical relapse. In the patient with histologic resolution and persistence of symptoms, another unrecognized cause for the diarrheal symptoms (eg, irritable bowel syndrome) or mucosal sampling error may have accounted for the discrepancy. Since this patient did have subsequent documentation of recurrent histologic disease, the latter explanation for the discordant findings is most likely. Multiple studies have now demonstrated that the subepithelial collagen band can disappear during therapy with antiinflammatory medication and that histologic improvement of the collagenous colitis is associated with clinical improvement (2, 5, 18–20). Our experience indicates that reversion to normal mucosa is a realistic expectation in many of these patients.

The cause of collagenous colitis and the reason for a thick collagen band in this form of mucosal injury and not others, such as inflammatory bowel disease or ischemia (2, 4, 22), is unknown. The triggering factor may cause not only mucosal injury but also dysfunction of the pericryptal myofibroblasts resulting in reduced cell turnover, a prolonged phase of cell maturity, and more than normal collagen production (6, 30–32). Immunohistochemical studies have demonstrated that the subepithelial collagen layer in collagenous colitis consists of types I and III collagens and fibronectin, in contrast to the basement membrane of the normal colon, which consists of type IV collagen, laminin, and fibronectin (2, 4, 26). Collagen types I and III have been associated with a reparative response to injury and inflammation (2, 26), and their presence may well reflect a more advanced or chronic stage of mucosal injury. Since the histologic appearance of microscopic colitis is distinguished from that of collagenous colitis by the absence of a subepithelial collagen band (21, 22), it may represent an earlier or less severe pattern of mucosal injury. Indeed, sequential biopsy assessments have documented the evolution of a collagen band on such a background (16). Similarly, gradual resolution of the inflammatory process and termination of the reparative response may result in the disappearance of the collagen layer and improvement of the mucosa to normal through a stage that resembles microscopic colitis. The histologic findings of microscopic colitis in conjunction with those of collagenous colitis in specimens from the colon proximal to the sigmoid and the demonstration of different histologic patterns in sequential specimens obtained from the same anatomic site support the hypothesis that microscopic colitis and collagenous colitis are manifestations of the same disorder at different stages.

Alternatively, the different histologic patterns from the same anatomic region at different times and from different anatomic regions at the same time may reflect the known patchy distribution of collagenous colitis (1–6) and the sampling variability that may occur when diagnosing and monitoring a mucosal disease associated with a normal endoscopic appearance. The absence of a subepithelial collagen layer under such circumstances may not reflect a transition from collagenous colitis to microscopic colitis but rather various histologic manifestations of the same disease and/or deficiencies in our ability to assess this disease consistently. Our findings may well justify a reconsideration of the diagnostic criteria for collagenous colitis and microscopic colitis if these are to remain separate entities. In the former condition, the presence of a subepithelial collagen band in any region of the bowel may be sufficient to establish the diagnosis thereafter regardless of concurrent or subsequent biopsy findings in the same or different regions of

the bowel that fail to show the collagen layer. In the latter instance, mucosal samples demonstrating absence of a collagen layer in every region of the bowel thereafter may be required to justify and sustain the diagnosis of microscopic colitis. Additional studies using serial colonoscopic examinations and universal mucosal sampling strategies will be necessary to establish the independent, individual identity of each of these conditions.

Relapse of collagenous colitis is well recognized (17, 33) and two of four patients in our study who were followed after histologic resolution did relapse. The reasons for relapse are uncertain, but they may reflect incomplete resolution of inflammatory activity, failure to eliminate or permanently disrupt the underlying pathogenic mechanisms, or exposure to the same or other triggering factors. In our patients, relapse occurred despite normalization of the colonic mucosa, suggesting that the latter two explanations are most likely. Immunologically mediated disorders are characterized by relapse since clinical expression can be fully suppressed during therapy while perpetuating mechanisms endure (34). The striking female predominance in collagenous colitis, the histologic similarities between it and celiac disease, and its association with other immunologic disorders suggest an autoimmune nature (2). As yet, however, there is no direct evidence that the disease is self-perpetuating. Alternatively, exposure to the same or other triggering agents may produce recrudescence by direct mucosal injury or by antigen presentation and stimulation of immunoreactivity (15, 16). Here again, however, there is no direct evidence to support the hypothesis that specific viruses, dietary factors, or luminal antigens are important in the genesis of the disease (3).

Unfortunately, we cannot fully exclude mucosal sampling error and incomplete histologic resolution of the disease as a factor in relapse. Although our patients with histologic resolution had documentation of normal mucosa in all biopsy specimens obtained from multiple anatomic sites, only two of these patients, one of whom relapsed after drug withdrawal, had undergone colonoscopy and universal mucosal sampling at the time of this follow-up to document normal mucosa throughout the colon. Other studies have indicated that the subepithelial collagen band is less pronounced in the distal colon, sigmoid, and rectum (2, 3, 25), and certainly our experience has underscored the variation of histologic findings in different regions of the colon, the higher frequency of normal mucosa in distal anatomic sites, and the propensity of rectosigmoid samples to underestimate the degree and nature of the colonic involvement. Consequently, we cannot exclude the possibility of residual collagenous colitis in other more proximal regions of the colon in our patients who relapsed. From a practical clinical standpoint, our observations underscore the importance of colonoscopy and random mucosal biopsies from the colon proximal to the sigmoid to confidently diagnose and monitor collagenous colitis.

The histologic features of collagenous colitis, microscopic colitis, and normal (or reactive) mucosa proved to be distinctive, as there was a high frequency of agreement among our gastrointestinal pathologists in the interpretation of the tissue changes. Consequently, the different histologic patterns that were described in different regions of the colon at the same time and in the same regions at different times probably reflected variations in the expression of the disease rather than inconsistencies in interpretation. Importantly, all of the histologic interpretations were based on tissue sections that had been stained with hematoxylin and eosin, and the value of the trichrome stain in enhancing diagnostic accuracy remains uncertain (25).

Pathophysiologic studies in collagenous colitis have demonstrated a profuse secretion of fluid and electrolytes within the colon and the likelihood of a diffusion barrier created by the subepithelial deposits of collagen (35). Disappearance of the collagen layer alone, however, may not be sufficient to alleviate the diarrheal symptoms if inflammatory activity persists within the mucosa. Indeed, patients with microscopic colitis have a markedly decreased colonic absorption of sodium and chloride as well as reduced chloride and bicarbonate exchange, and they may have symptoms that are indistinguishable from those of patients with the subepithelial collagen layer (36). In our experience, diarrheal symptoms resolved predominantly in those who had reverted to normal mucosa, and we believe that this histologic end point is desirable and achievable.

In summary, our findings indicate that resolution and relapse occur in collagenous colitis and histologic assessment is a reasonable measure of disease activity; histologic changes can vary from site to site and from time to time as a result of sampling variability or disease in transition; adequate tissue sampling is important especially above the rectosigmoid; and there is acceptable agreement among gastrointestinal pathologists about the histologic diagnosis of collagenous colitis.

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