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Collagenous Colitis: Histopathology and Clinical Course

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Objectives: **Collagenous colitis is a chronic diarrheal disease characterized by a normal or near-normal mucosa endoscopically and microscopic inflammation in the lamina propria, surface epithelial injury and a thick subepithelial collagen layer. The symptoms of collagenous colitis vary in duration and intensity, and long periods of remission have been described, but long-term follow-up data are limited. Our goal was to determine the natural clinical history of collagenous colitis and to determine whether there was a relationship between histopathologic changes and course of disease.** ***Methods:*** **Cases were identified at the University of Michigan Hospitals using surgical pathology records before 1992. All charts, including medical records from other hospitals, were reviewed, and a telephone interview was conducted with each locatable patient (pt). Biopsy specimens were reviewed by two pathologists for degree of collagen layer thickness, epithelial damage, and inflammation.** ***Results:*** **There were 31 patients (26 F, 5 M) with a mean age of 66 yr (range 33–83) and a mean duration of symptoms of 5.4 yr at the time of diagnosis. Of the 31 patients, 18 (56%) had some form of arthritis, and 22 (71%) were using NSAIDS regularly at the time of diagnosis. Follow-up interviews were conducted at least 2 yr after diagnosis (mean 3.5 yr, range 2–5 yr) with 27 of 31 patients (3 could not be located, 1 died). Two definable groups of patients were identified: (1) those with either spontaneous or treatment-related symptom resolution (63%), and (2) those with ongoing or intermittent symptoms requiring at least intermittent therapy (37%). There was no significant difference between the two groups with regard to sex, age, associated diseases, and use of medications. Patients with symptom resolution (mean duration 3.1 yr) had been treated with antidiarrheals (6), sulfasalazine (3), discontinuation of NSAIDS (3), reversal of jejunoilial bypass (1), or nothing (4). Those with ongoing symptoms experienced a wide range of symptom severity. Two required only antidiarrheals, but five required or failed steroids, azathioprine, or sandostatin. There was no significant difference in collagen thickness, epithelial damage, and inflammation between the two groups, but Paneth cell metaplasia was seen more often in those with ongoing symptoms. In 24 of 27 patients, diagnostic changes were present in left-sided biopsies.** ***Conclusions:*** **In our cohort of patients, 63% had lasting resolution of symptoms after a mean 3.5 yr follow-up. There was a high incidence of arthritis and NSAID use in our population, but there was no relationship between these entities and clinical course or histology. Initial histology, except possibly for Paneth cell metaplasia, did not reliably predict severity or course of disease. Finally, although variable in clinical presentation, treatment-free remissions are common in collagenous colitis.**

INTRODUCTION

Collagenous colitis is a chronic diarrheal disease first described in 1976 by Lindstrom. He reported a single case of a middle-aged woman with cramps, abdominal pain, and chronic diarrhea (1). The colon appeared normal endoscopically, but biopsies revealed a distinct, thickened layer of subepithelial collagen. Since then, hundreds of cases of collagenous colitis have been reported and colonoscopists now know to obtain biopsies routinely in patients presenting with unexplained chronic diarrhea, even if the mucosa appears normal.

The disease is also histologically characterized by a chronic inflammatory cell infiltration of the lamina propria of variable intensity and damage to the surface epithelium, accompanied by excessive intraepithelial lymphocytes. Although the thickened collagen layer may not play the primary role in the pathogenesis of collagenous colitis, it is this finding that identifies and defines the disease and distinguishes it from similar diarrheal diseases such as lymphocytic colitis (2).

During the last 20 yr, the presenting clinical features of collagenous colitis have been well described, but there is only limited data describing the long-term clinical course of this disorder. Our goal was to evaluate the natural clinical history of collagenous colitis and to determine whether there is a relationship between specific histopathologic features and course of disease.

METHODS

Thirty-one cases of collagenous colitis before 1992 were identified from the records of the Department of Pathology at the University of Michigan hospitals. All specimens were

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reviewed retrospectively by two pathologists, including an experienced gastrointestinal pathologist, for degree of collagen layer thickness, epithelial damage (mild, moderate, or severe), lamina propria inflammation (mild or severe), presence of eosinophilia in the lamina propria, and Paneth cell metaplasia at the base of the crypts. The diagnosis of collagenous colitis was confirmed by the finding of a thickened subepithelial collagen layer in the appropriate histologic setting as mentioned above (3).

The hospital medical records and records from referring physicians were examined to determine demographic data, onset, and type of symptoms, associated diseases, medications, and all gastrointestinal evaluations and treatments. Subsequently, follow-up data was obtained through medical records and via a telephone interview using a questionnaire. All telephone interviews were conducted a minimum of 2 yr from the time of initial biopsy proven diagnosis. The data was analyzed using the Student's *t* test or 2-sided Fisher's exact test.

RESULTS

Clinical

Of the 31 patients with collagenous colitis, there were 26 women (85%) and 5 men with a mean age of 66 yr (range 33–83 yr). The mean duration of symptoms before diagnosis was 5.4 yr (range 0.1–25 yr). Of the 31 patients, 18 (56%) had some form of arthritis, and 22 patients (71%) used NSAIDS regularly at the time of diagnosis. Four patients had hypothyroidism, two had diabetes, one had myasthenia gravis, and one had Sjögren's syndrome. Five patients (16%) had a history of other conditions that may have contributed to diarrheal symptoms including partial bowel resection (2), celiac sprue, *C. difficile* infection, and jejunoileal bypass.

We obtained follow-up clinical data after an interval of at least 2 yr (mean 3.5 yr, range 2–5 yr) from diagnosis on 27 of the 31 patients. One was deceased and three could not be located. Subsequently, two broad subgroups of patients were identified: (1) 63% had long-lasting symptom resolution either spontaneously or after treatment; and (2) 37% had ongoing disease requiring constant or intermittent therapy. There was no significant difference between the two groups when the variables age, sex, associated diseases, and use of NSAIDs were examined. The "resolved" group had experienced symptoms for a mean of 3.5 yr (median 1.0 yr, range 0.1–20 yr) compared with 8.5 yr (median 7.5 yr, range 0.2–25 yr) for the "ongoing" group ($p = 0.09$ for means).

Patients with symptom resolution (mean duration of symptom resolution = 3.1 yr) had been treated with antidiarrheals (6), sulfasalazine (3), discontinuation of NSAIDs (3), reversal of jejunoileal bypass (1), or nothing (4). After the diagnosis was established, the mean duration to symptom resolution was 1.5 months (0.3–4 months). There was considerable heterogeneity among the 10 patients in the "ongoing" group ranging from mild, occasional symptoms controlled with intermittent use of antidiarrheals to persistent symptoms despite continuous immunosuppressives (Table 1). Half of these patients require steroids or other immunosuppressives for control of diarrhea. Follow up colonoscopies with biopsies were not obtained routinely.

Histopathology

The colorectal biopsy specimens from all patients in both the "resolved" and "ongoing" groups were reviewed in a blinded manner by two pathologists who had no knowledge of the patients' clinical history or subsequent course (Table 2). There was no statistically significant difference in collagen layer thickness or lamina propria cellularity (inflammation) between the two groups. However, the most intense collagen deposition and inflammation occurred in two "ongoing" patients, and all patients in the "ongoing" group had severe inflammation. There was no difference in severity of epithelial damage between the two groups. Excess eosinophils were noted in slightly more than 50% of patients in both groups and was predominantly located in the basal half of the lamina propria. Paneth cell metaplasia was seen in 60% of those with "ongoing" symptoms but only 12% of those in the "resolved" group ($p = 0.025$). Biopsies were obtained from both the right and left sides of the colon in 23 of the 27 patients. The degree of histologic abnormality was approximately equivalent in both sides of the colon in all but five patients (collagen thickness and inflammation greater on the right in three and greater on the left in two). In one "ongoing" patient, the rectum was normal, and, in one "ongoing" and one "resolved" patient, there was very little extra collagen on the left-sided biopsies. Thus in 24 of the 27 patients, the diagnosis of collagenous colitis could be made on the basis of left-sided biopsies alone.

DISCUSSION

Collagenous colitis is an inflammatory disease of unknown etiology characterized by chronic diarrhea and a thickened band of subepithelial collagen. Our patients were predominantly elderly women typical of those previously described in the literature. More than 80% are female with an average age of approximately 60 yr (3–6). The majority of our patients had arthritis, several had autoimmune diseases, and over two-thirds were taking NSAIDs.

The association of collagenous colitis with a variety of immune disorders and its response to sulfasalazine and steroids suggests that this entity, similar to ulcerative colitis and Crohn's disease, may be an autoimmune inflammatory disease (3, 7, 8). However, the pattern of HLA antigens has been shown to be no different in collagenous colitis patients than in a control population (9). A recent report showing that fecal stream diversion induces both a clinical and histologic remission in collagenous colitis suggests that a toxic luminal factor or factors may be of pathogenic importance (10). The inciting luminal factor may produce an inflammatory reaction in the colonic mucosa which, in time, leads

TABLE 1
Therapy in Patients with "Ongoing" Symptoms

Patient	Treatment Failures	Baseline Management	Rate of Relapse	Treatment of Relapse
1	Cholestyramine, loperamide, sulfasalazine	Prednisone	Whenever prednisone is withdrawn	Prednisone
2	Loperamide	None if no flare	Single flare in 3 yr	Loperamide or diphenoxylate
3	Sulfasalazine	Loperamide	None for 2 yr	Prednisone taper
4	Loperamide, psyllium	Mesalamine, prednisone	Every 2 yr	Tincture of opium
5	Sulfasalazine	Sandostatin	Mild flare every 2–3 months	Loperamide, hyoscyamine
6	Metronidazole, sulfasalazine	None if no flare	Mild flare once a month	Loperamide, hyoscyamine
7	*Pancreatic enzymes, cholestyramine,* sulfasalazine	*Azathioprine (previously on prednisone)*	*Every few months*	*Loperamide*
8	Prednisone, sulfasalazine, sandostatin	None	Chronic diarrhea	Nothing
9	Sulfasalazine	Mesalamine, loperamide	None for ~2 yr	Prednisone
10	Azathioprine, mesalamine, sulfasalazine	Prednisone, mesalamine	Chronic diarrhea	Prednisone

TABLE 2
Colorectal Histopathology

	Resolved Symptoms (n = 17)	Ongoing/Recurrent Symptoms (n = 10)
Epithelial damage		
Mild	5 (29%)	1 (10%)
Moderate	4 (24%)	4 (40%)
Severe	7 (41%)	5 (50%)
Inflammation		
Mild	5 (29%)	0 (0%)
Severe	11 (65%)	10 (100%)
Eosinophilia	10 (59%)	6 (60%)
Paneth cell metaplasia	2 (12%)	6 (60%)

to deposition of subepithelial collagen (7). The use of NSAIDs has been linked to collagenous colitis and may conceivably play a causative role according to a case-control study by Riddell *et al.* (4, 11). Anecdotal cases suggest that withdrawal of NSAIDs is associated with improvement in diarrheal symptoms (4, 11). The 71% incidence of NSAID use in our population is similar to the 61% incidence reported in the series by Riddell *et al.* (4). Although three of our patients seemed to improve after discontinuing NSAIDs alone, our numbers are too small to make any conclusion about a causal relationship.

Almost two-thirds of our patients had complete resolution of symptoms. Follow-up biopsies were not systematically obtained in most patients in our series, but reportedly, histologic resolution may frequently accompany symptomatic resolution (5, 8, 11–13). A few received anti-inflammatory therapy in the form of azulfidine, but most were treated nonspecifically with antidiarrheals, discontinuation of NSAIDs, or nothing at all. The duration of symptoms before diagnosis was highly variable and did not accurately predict which patients would experience persistent or recurrent symptoms ("ongoing"), although these patients had a tendency toward a longer duration of symptoms than the "resolved" group. Prolonged remission or "cure" of collagenous colitis after short duration or no therapy has not been previously well emphasized. Spontaneous resolution of collagenous colitis or resolution after symptomatic treatment (antidiarrheals) or withdrawal of NSAIDS has been noted previously (12–15). Although these patients are felt to represent the minority of those with collagenous colitis, we found that nearly 50% of our patients fit this description (16). Extended remission after treatment has also been noted (5, 6, 17). Our 63% of patients without symptoms off therapy after 3 years is similar to a recent series reporting 52% after the same length of follow-up (18). It is possible that with even longer follow-up, a few patients may relapse. Even in the "ongoing" group, 4 of the 10 patients require minimal or no therapy and relapse infrequently. Only 6 of 27 (22%) of the entire group require continuous therapy or have persistent symptoms. These data suggest that prolonged medical therapy is often not necessary for collagenous colitis. Once a remission is established, it seems appropriate to attempt withdrawal of therapy as a recent empiric algorithm suggests (16).

We did not find that histopathologic changes on initial biopsy specimens were reliably predictive of the subsequent clinical course. Collagen layer thickness was the same in both groups. However, it is likely based upon histologic studies in both collagenous and lymphocytic colitis, that surface cell injury and inflammation and possibly lamina propria cellularity and not collagen layer thickness are responsible for diarrheal symptoms (2). Those patients who developed ongoing or recurrent symptoms were significantly more likely to have Paneth cell metaplasia and tended to have somewhat more lamina propria inflammation and epithelial damage than those whose symptoms later resolved. Paneth cell metaplasia may, therefore, be a useful marker to predict more persistent or severe disease, but it is not dependable. We cannot discount the possibility that a larger series of patients may show a statistically significant difference between these two groups with regard to these other histologic features as well.

The histologic findings of collagenous colitis may be distributed in a patchy manner with less intense involvement distally in the colon (3, 19). Small series suggest that proctosigmoidoscopic examination may miss the diagnosis in up

to 40% of patients (5). We found that left-sided biopsies alone would have been sufficient to make the diagnosis of collagenous colitis in 89% (24 of 27) of our patients. However, because rectal and sigmoid biopsies often were not taken and separated from other left-sided biopsies, we cannot be certain how often the distal left colon is less involved than the proximal left colon. A recent large review of colonoscopic and flexible sigmoidoscopic biopsy specimens found that only 5 of 97 (5%) patients had nondiagnostic rectosigmoid biopsies (20). So it appears that although involvement is less intense in the left colon, biopsies obtained by flexible sigmoidoscopy should be sufficient to make the diagnosis of collagenous colitis most of the time, especially if biopsies are obtained from the descending colon. A colonoscopy may be required if sigmoidoscopic biopsies are nondiagnostic and a high index of clinical suspicion remains.

In summary, we found that the majority of patients diagnosed with collagenous colitis had spontaneous or treatment-induced sustained resolution of symptoms. Although there was a tendency for those with ongoing symptoms to have a longer history of symptoms before diagnosis and, on biopsy, to have Paneth cell metaplasia and severe inflammation in the lamina propria, clinical variables and initial histology did not reliably predict severity or course of disease.

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