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Collagenous colitis: a retrospective study of clinical presentation and treatment in 163 patients

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Abstract

***Background*—Data on collagenous colitis have been based on a limited number of patients.**

***Aims*—To obtain more information on this disease from a register set up at Örebro Medical Center Hospital.**

***Patients and methods*—Twenty five Swedish hospitals have contributed to this patient register, which comprises 163 histopathologically verified cases. Clinical data were retrospectively analysed.**

***Results*—Collagenous colitis followed a chronic intermittent course in most cases (85%) with a sudden onset in 42%. Symptoms were chronic watery diarrhoea, often nocturnal (27%), abdominal pain (41%), and weight loss (42%). Sixty six patients (40%) had one or more associated diseases. Routine laboratory data were mostly normal. The median age at diagnosis was 55 (range 16–86) years, but 25% of the patients were younger than 45 years. Seven patients died of unrelated diseases. The response rate for sulphasalazine was 59%, and 50% and 40% for mesalazine and olsalazine. Prednisolone was most effective with a response rate of 82%, but the required dose was often high and the effect was not sustained after withdrawal. Antibiotics were efficient in 63%. Cholestyramine and loperamide had response rates of 59% and 71% respectively.**

***Conclusions*—Collagenous colitis follows a chronic continuous course. Symptoms can be socially disabling, but the disease does not seem to have a malignant potential. A plan for the treatment of a newly diagnosed patient with collagenous colitis is proposed.**

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Collagenous colitis, described in 1976 by Lindström,[1] is characterised clinically by chronic watery diarrhoea, and histopathologically by a thickened subepithelial collagen layer adjacent to the basal membrane, infiltration of the lamina propria with inflammatory cells, epithelial lesions, and infiltration of the epithelium with lymphocytes.[2] Today, collagenous colitis is widely accepted as an entity of its own, and by the end of 1992, 446 patients with collagenous colitis had been described in the medical literature (CG Lindström, personal communication).

The clinical features and treatment of the disease are mainly based on case reports or small uncontrolled series. Only one controlled study has been undertaken, on corticosteroid treatment,[3] as the few patients at each hospital have limited larger controlled trials on treatment.

At our hospital, a register of patients with collagenous colitis has been established during the past six years. The present study presents retrospectively evaluated data on clinical features and medical treatment.

Methods

PATIENTS

A register of patients with collagenous colitis was established in 1989 at Örebro Medical Centre Hospital. At first it was limited to patients diagnosed in this hospital, but since 1992 records from other hospitals have been included after consent of the patients. Twenty four hospitals submitted the medical records of their patients with collagenous colitis to us, or allowed us to scrutinise the notes at the hospital. Registration of data for this study was concluded by December 1995. The register was approved by the Swedish Data Inspection Board.

DIAGNOSTIC CRITERIA

All biopsy material was re-evaluated by one of us (SE), and the following histopathological criteria in a van Gieson stained specimen had to be fulfilled: (1) a subepithelial collagen layer with a thickness of at least 10 μm on a well oriented section of the mucosa – that is, a section where at least three adjacent crypts were cut in their vertical plane; (2) the presence of lymphocytic infiltration in the epithelium or lesion in the form of detachment, flattening, or vacuolisation of the epithelium; (3) inflammation of the lamina propria with infiltration of predominantly plasma cells and lymphocytes.[2]

These histopathological features, together with the main symptom – chronic water diarrhoea – constituted the diagnostic criteria.

CLINICAL DATA

All clinical data were evaluated retrospectively. The age of the patient at the time of histopathological diagnosis and at the time of onset of the disease were registered. Whether the onset of diarrhoea was sudden (within a few days) or insidious and stool frequency were noted at the time of the diagnosis. Any history of abdominal pain was registered, but this could not be specified regarding location or intensity.

Weight loss, quantified if possible, and symptoms of fatigue were noted. The longterm course of the disease was evaluated individually as single episode, chronic intermittent, or chronic continuous. Disease activity during pregnancy and associated diseases of inflammatory or autoimmune origin were registered.

LABORATORY DATA

Blood tests were recorded if taken within two weeks of the date of diagnosis. The following variables were recorded with normal ranges given in parentheses: erythrocyte sedimentation rate (women 2–15 mm, men 2–10 mm) and haemoglobin (women 115–140 g/l, men 135–165 g/l). Serum albumin (37–46 g/l), alkaline phosphatases (2·0–5·0 μkat/l), alanine transaminase and aspartate transaminase (0·2–0·8 μkat/l), platelet concentration (180–350×10^9/l), and creatinine (60–115 μmol/l). A retention on day 7 of less than 10% of the administered doses of radioactivity was considered diagnostic for bile salt malabsorption when testing with the selenium-75-homocholic acid taurine test (SeHCAT test).

ENDOSCOPY

The macroscopic appearance of the mucosa during colonoscopy or sigmoidoscopy was registered.

TREATMENT

Medication given for collagenous colitis was evaluated, as well as medication possibly influencing the disease – namely, non-steroidal anti-inflammatory drugs (NSAIDs) and cytostatic treatment. The effect was evaluated retrospectively, and relied on the change or lack of change in the stool frequency. If the medication improved the patients' diarrhoea, it was registered as having an 'effect'. If the medication did not have any impact on the patients' diarrhoea, it was registered as having 'no effect'. If side effects (nausea, abdominal pain, diarrhoea, taste sensation) or idiosyncrasies (fever, skin rash, agranulocytosis) occurred, they were registered as 'adverse effects'. If the effect was not mentioned, or there was any doubt of the outcome, or mixed medication was given, the drug was not included in the analysis.

Data on surgical treatment in nine patients with medically intractable diarrhoea have been described earlier.[4]

STATISTICS

Clinical data are presented as medians (range); laboratory data are presented as means. In retrospective studies not all information is available in all medical notes. Therefore, the percentages in various respects have been calculated from the number of patients for whom medical notes confirmed or denied the occurrence of a sign or symptom. This explains the varying numbers in different Tables.

Results

PATIENTS

Histopathological specimens from 196 patients suspected of having collagenous colitis were re-evaluated. A total of 163 patients fulfilled the above mentioned criteria, and 33 were excluded. Twenty of these 33 cases had some other form of microscopical colitis, six had unspecific colitis, one had acute colitis and *Salmonella species* in faecal culture, and six had normal colonic mucosa.

CLINICAL DATA

Age and sex ratio

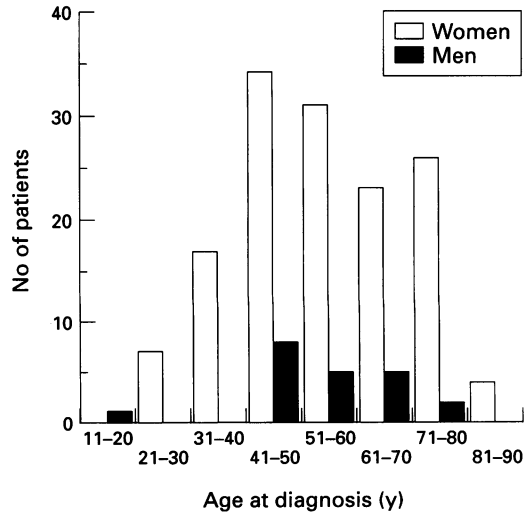
The median age at the time of diagnosis was 55 (18–87) years, equal for men and women. Of the 163 patients, 142 were women and 21 were men, yielding a female:male ratio of 6·8:1. The Figure shows the age distribution at the time of diagnosis. Forty patients (25%) were diagnosed before the age of 45. The median age at the time of onset of symptoms was 48 (16–86) years. The duration of symptoms from onset to diagnosis varied considerably (median 47 (1–421) months). The median follow up time was three (0–16) years.

Mode of onset and clinical course (Table I)

For 48 patients a sudden onset was mentioned; 66 had an insidious onset and for 49 patients the mode of onset was not specified in the records. Two patients have so far only had a single episode – that is, longlasting remission was obtained within three months. One experienced remission spontaneously and one after treatment with metronidazole. Ninety patients had a chronic intermittent course and 14 patients experienced a chronic continuous course; in 57 patients the course was not described.

Symptoms (Table I)

All patients had diarrhoea. In 131 of 163 patients the stool frequency was reported at the time of diagnosis. The median value was six



Distribution of patients in relation to age at diagnosis.

TABLE I *Clinical data in 163 patients with collagenous colitis*

	n (%)
Onset (n=114):	
Sudden	48 (42)
Insidious	66 (58)
Course (n=106):	
Single episode	2 (2)
Chronic intermittent	90 (85)
Chronic continuous	14 (13)
Symptoms (n=153):	
Weight loss*	64 (42)
Abdominal pain	62 (41)
Nocturnal diarrhoea	41 (27)
Fatigue	21 (14)
Meteorism	12 (8)
Stools per day (n=131):	
≤3	16 (12)
4–9	86 (66)
≥10	29 (22)

*Median value 6 kg, range 3–20 kg. n=Number of patients on whom information is available.

(1–23) stools per day. Sixteen patients had ≤3 stools per day, 86 patients had four to nine, and 29 patients had 10 or more. Forty one patients (27%) had nocturnal diarrhoea.

Recordings regarding symptoms other than diarrhoea were available in 153 cases. Unspecified abdominal pain was experienced by 62 patients, fatigue occurred in 21, and meteorism in 12. Weight loss was registered in 64 cases, and quantified in 40 (median 6 (3–20) kg).

Disease activity during pregnancy

Five women became pregnant after the diagnosis of collagenous colitis. All experienced clinical remission during pregnancy and remained in remission some months after delivery.

Associated diseases (Table II)

Sixty six patients (40%) had one or more associated diseases of inflammatory or autoimmune origin. The four most frequent were rheumatoid arthritis (n=16), thyroid disorders (n=14), coeliac disease (n=13), and diabetes mellitus (n=9). Four patients had a concomitant inflammatory bowel disease, which was histopathologically in remission at the time of the diagnosis of collagenous colitis. Three had Crohn's disease diagnosed one, four, and 32 years before the diagnosis of collagenous colitis on resected specimens from the colon (n=2) or ileum (n=1) with typical findings such as granulomas and transmural inflammation. One patient had ulcerative proctitis diagnosed eight years before collagenous colitis.

Of the 66 patients with associated diseases, 48 patients had one associated disease, 15 patients had two, two patients had three, and one patient had four.

TABLE II *Associated diseases in 163 patients with collagenous colitis*

	n (%)
Rheumatoid arthritis	16 (10·0)
Seropositive	6
Seronegative	5
Serum not examined	5
Thyroid disorders	14 (8·6)
Hyperthyroidism	8
Hypothyroidism	4
Goitre	2
Coeliac disease	13 (8·0)
Asthma/allergy	10 (6·2)
Diabetes mellitus	9 (5·5)
Insulin dependent	6
Non-insulin dependent	3
Chronic gastritis	4 (2·5)
Crohn's disease	3 (1·9)
Ulcerative proctitis	1 (0·6)
Sjögren's syndrome	3 (1·9)
Psoriasis	3 (1·9)
Raynaud's disease	3 (1·9)
Polymyalgia rheumatica	2 (1·2)
Dermatitis herpetiformis	2 (1·2)
Mb Bechterew	2 (1·2)
Sarcoidosis	1 (0·6)
Alopecia	1 (0·6)
Systemic lupus erythematosus	1 (0·6)

Mortality

Seven patients had died at a median age of 66 (55–79) years of diseases not related to collagenous colitis. These were pulmonary fibrosis with respiratory insufficiency (n=2), myocardial infection (n=2), cerebrovascular lesion (n=1), lung cancer (n=1), and relapse of acute lymphatic leukaemia (n=1).

LABORATORY DATA

The erythrocyte sedimentation rate was recorded for 44 patients. The mean for women and men was 25 and 12 mm respectively. The mean concentrations of haemoglobin, serum albumin, alkaline phosphatases, alanine transaminase, aspartate transaminase, platelet concentration, and creatinine were normal. Fifteen of the patients treated with cholestyramine were tested with the SeHCAT test. Ten had bile salt malabsorption.

ENDOSCOPY

In 105 patients (71%), normal appearing colonic mucosa was reported, and in 42 patients (29%), non-specific abnormalities such as oedema, erythema, or abnormal vessel patterns were seen, while in 16 patients the macroscopic appearance was not reported.

TREATMENT

Table III shows the data on treatments. In most patients more than one treatment regimen was tried. Adverse reaction to sulphasalazine occurred in 45 of 108 (42%) treatments. Treatment with prednisolone often resulted in prompt improvement, but relapse usually occurred only days after treatment was discontinued. Two

TABLE III *Retrospective evaluation of treatment in collagenous colitis*

	No of patients	Effect	No effect	Adverse effects
Sulphasalazine	108	37	26	45
Mesalazine	16	8	8	0
Olsalazine	15	4	6	5
Prednisolone	39	32	6	1
Budesonide*	2	2	0	0
Metronidazole	44	24	16	4
Erythromycin	15	10	4	1
Penicillin	8	8	0	0
Cholestyramine	44	26	17	1
Mepacrine	19	10	7	2
Loperamide	69	49	18	2

*One controlled ileal release and one controlled colon release.

patients received budesonide, one with controlled ileal release and one with controlled colonic release; both had relief from symptoms on this treatment. Relapse was also noticed in responders after treatment with antibiotics, but the interval between discontinuation and relapse was usually longer than after treatment with corticosteroids (weeks rather than days). Of the 26 patients who responded to cholestyramine treatment, 10 had a pathological and five a normal SeHCAT test. Loperamide often had to be given at high dosage (4 mg thrice daily or more) to be effective.

One patient with pulmonary cancer and one with breast cancer were treated with fluorouracil alone or in combination with mitoxantrone and folic acid. Two patients received low dose methotrexate for rheumatoid arthritis. Clinical improvement in collagenous colitis was seen in all four patients during these treatments.

Information on treatment with NSAIDs were available in 104 patients. Thirty five of these had taken NSAIDs regularly or for limited intervals.

Discussion

Only a few larger studies of patients with collagenous colitis have been presented up to now. The latest published review, of The Johns Hopkins Collagenous Colitis Registry, contains 107 patients.[5] Pierrugues *et al* reviewed in 1989 their experience of 40 patients,[6] and Zins *et al* have recently presented some data from 172 patients.[7]

The median age at diagnosis in our study of 55 years and the sex ratio of 6·8:1 is in accordance with the Johns Hopkins experience.[5] However, 40 (25%) of the 163 patients were diagnosed before the age of 45 years. It is usually not well known that substantial numbers of patients who acquired collagenous colitis are young, but our findings clearly illustrate that collagenous colitis must be considered also in young people with chronic watery diarrhoea.

The onset of collagenous colitis might be sudden. Forty eight patients described it as such: some could even mention the exact date, similar to the onset of an infectious gastroenteritis. The type of onset was described by 114 patients, implying sudden onset in 48 of 114 (42%). However, this must be regarded as a maximum percentage, as a sudden onset is more likely to be mentioned than an insidious one. If none of the 49 patients with an unknown type of onset had a sudden type, the frequency would be 48 of 163 (29%), which would be the minimum percentage.

In two patients longlasting remission was acquired within three months of onset. Most (85%), however, had a chronic intermittent course. Watery diarrhoea is regarded as the primary symptom in collagenous colitis, and only one case with chronic obstipation has been reported.[8] As all patients in our survey were investigated because of chronic watery diarrhoea we cannot comment on this point. Nocturnal diarrhoea was fairly common in our patients (27%), but a more frequent occurrence (68%), was reported in a study of 19 patients.[9]

Weight loss occurred in 42% of the patients, and it was occasionally pronounced (one patient lost more than 20 kg). Evidence of malabsorption in the form of steatorrhea has been reported,[10 11] and could be one of the explanations for the weight loss. Otherwise the cause is unknown. Serious dehydration was seen in one patient only, although 22% had more than 10 watery stools per day. Dehydration has been reported as a possible contributing factor in a patient who died,[12] but this seems to be a rare complication. Abdominal pain is common.[5 13] In our study 41%, and in another recent study[9] 79%, had abdominal pain. Schub *et al* who studied motility in collagenous colitis, found that abdominal pain was not due to increased motility in the colon.[14] In the present study 21 patients (14%) complained of fatigue; 67% of these patients had either some associated systemic disease or non-specific arthralgias, which might at least partly explain their fatigue.

The variation in duration of symptoms from the onset of the disease to the time of the histopathological diagnosis was very large: one month to 35 years. We have shown in a previous study that this interval decreased considerably in our catchment area during 1984–93, most probably because of an increased awareness of collagenous colitis and an increased biopsy rate during endoscopy.[15]

Five patients experienced remission during pregnancy and even some months after delivery. Collagenous colitis is more common in women than men which, together with the effect of pregnancy on symptoms, indicates that hormonal changes may influence the course of the disease and perhaps are of pathogenetic importance. Sex hormones and pregnancy have been shown to have a modifying effect on the immune system and autoimmune disease; thus collagenous colitis may be an example of the greater female susceptibility to autoimmune diseases.[16 17]

No patient in our register had died from collagenous colitis and it does not seem to have a malignant potential.[5] The course in most cases is chronic, and often troublesome, but benign.

Laboratory tests were normal. Earlier studies have come to the same conclusion, except that patients might have a slightly raised erythrocyte sedimentation rate, mild anaemia, or peripheral eosinophilia.[5 18] The mean erythrocyte sedimentation rate in our study was 24 mm. For clinical purposes this has little relevance. In earlier studies we found that the serum IgM concentration was significantly increased in collagenous colitis and the serum concentration of P-III-NP, a product of collagen III synthesis, did not alter.[19 20] As in most series of microscopical colitis no endoscopic changes were noted in most patients. Changes, always subtle were reported in only 29% thus the only means of diagnosis for collagenous colitis is colonoscopy biopsies, although an increased concentration of IgM might be an indicator of the disease.

Patients with collagenous colitis often have concomitant diseases of autoimmune origin.[6 16 21 22] In our study 66 patients (40%) had one or more associated diseases. The fact that the disease is associated with other diseases of autoimmune or suspected autoimmune origin, is another indication for collagenous colitis being an autoimmune disease itself.[23 24] The association between coeliac disease and collagenous colitis has been noted, but a common aetiology is questioned.[2 7 25] However, if a patient with collagenous colitis responds poorly to treatment, it is important to exclude coeliac disease as a cause of treatment failure. Three of the patients in our register had Crohn's disease diagnosed before the diagnosis of collagenous colitis. Two earlier reports have described the development of Crohn's disease before or after collagenous colitis.[26 27] The association between the two diseases might be coincidental.

Retrospective assessment of the efficacy of treatment has several limitations and cannot be compared with clinical trials. Therefore our results must be interpreted with caution.

Sulphasalazine was the most often prescribed treatment. Side effects to sulphasalazine seemed to occur more often than when treating ulcerative colitis. However, 59% of those who tolerated the drug had benefit from it. Earlier reports on the effect of treatment with sulphasalazine have been based on small numbers, with response rates between 25% and 75%.[9 10 18 28 29] Mesalazine and olsalazine seem to be somewhat less efficient. The response rates in our study were 50% and 40% respectively. Both have been tried previously in small series and case reports, with varying results.[29–33]

Prednisolone was the most effective treatment, which is also supported by other reports.[3 9] Thirty two patients (82%) responded to prednisolone. However, the effect was not sustained. Relapse often occurred early after withdrawal, and the dose required to maintain remission was often unacceptably high, at more than 20 mg per day. Oral budesonide, with its lesser systemic effects, may be an alternative. Our experience is limited to two patients, both of whom responded.

Various antibiotics and mepacrine hydrochloride seem to be helpful in collagenous colitis, and generally with very few side effects. Metronidazole and erythromycin were the most often prescribed drugs, and most patients (55% and 67%, respectively) responded well. Penicillin G was effective in all eight patients treated. Half of the patients showed benefit from treatment with mepacrine hydrochloride. Mepacrine has both antibiotic effect and an inhibiting effect on arachidonic acid synthesis.[34 35] Effects of antibiotics and mepacrine in collagenous colitis have been reported,[7 34 35] supporting the hypothesis that collagenous colitis might be a disease initiated by a microbiological agent. The effect of sulphasalazine might also partly depend on its antimicrobial property via the sulphur moiety. The sudden onset of collagenous colitis in some cases supports the theory of infection.

Cholestyramine was effective in 26 (59%) patients, and was generally well tolerated. Cholestyramine binds various substances – for example, bile salts and bacterial toxins – which both could be of pathophysiological importance in collagenous colitis. The involvement of bile salts as part of the pathophysiology has been suggested by two groups who reported on bile salt malabsorption in patients with collagenous colitis,[10 36] but this was questioned by a third group.[37] In our study, 15 of the patients who responded to cholestyramine had been examined by the SeHCAT test and 10 had signs of bile salt malabsorption. Thus five patients responded to cholestyramine without having signs of bile salt malabsorption. In such cases the effect of cholestyramine could be due to absorption or inactivation of bacterial toxins. This mechanism has been suggested in a case report.[38] Our finding that faecal stream diversion in collagenous colitis induces clinical and histopathological remission supports the view that a luminal factor may be of aetiological importance.[39]

Loperamide was prescribed to 69 patients in this study. Seventy one per cent benefited from this, and serious side effects were not reported. In some earlier reports loperamide had no effect,[40 41] but in two recent reviews of collagenous colitis non-specific antidiarrhoeal medication is recommended as the primary treatment.[5 18] Our results support this view.

In four patients cytostatic treatment was given for concomitant diseases. In two patients diarrhoea disappeared after treatment with methotrexate for rheumatoid arthrtitis. A clinical effect of methotrexate in inflammatory bowel disease has been suggested earlier.[42] The two patients who received treatment with fluorouracil with or without mitoxantrone and folic acid for malignant disorders also had a clear improvement of the bowel symptoms. The clinical implication is not obvious, but the effect of cytostatic treatment in collagenous colitis is of interest.

Thirty five of 104 patients with collagenous colitis (34%) had regular or sporadic treatment with NSAIDs. It has been claimed that NSAIDs could be an aetiological factor in collagenous colitis,[43 44] but this idea was contradicted by others.[45 46] NSAIDs are usually prescribed for associated arthritis or arthralgia, which makes it difficult to conclude whether NSAIDs cause or are the consequence of collagenous colitis. Obviously, most patients with collagenous colitis do not use NSAIDs, and therefore it can only be one of several aetiological factors.

On the basis of this retrospective study we suggest that the following treatments should be tried in a newly diagnosed patient with collagenous colitis:

(1) Antidiarrhoics – for example, loperamide (a dose of 4 mg thrice daily may be required for loperamide).

If no response:

(2) Sulphasalazine: it might be wise to titrate the dose for one or two weeks to reduce adverse events. In cases of intolerance to sulphasala-

zine, mesalazine and olsalazine are other options.

If still no response:

(3) Cholestyramine: supplement with vitamin may be needed during longterm treatment.

If still no response:

(4) Prednisolone: this drug usually has a prompt effect but symptoms reappear soon after withdrawal, and often a daily dose of ⩾20 mg is needed. It is possible that budesonide with its lesser systemic side effects is an alternative.

If still no response:

(5) Antibiotics such as metronidazole, erythromycin, or penicillin G or mepacrine often relieve symptoms for some weeks, but seldom give a longlasting effect.

(6) Immunosuppressant therapy such as methotrexate might have an effect. However, these drugs have potentially serious side effects and a split ileostomy is the recommended option in medically resistant cases.

In patients resistant to treatment it is important to exclude concomitant causes of diarrhoea – for example, coeliac or thyroid disease.

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