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Collagenous colitis without diarrhoea at diagnosis – a follow up study

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ABSTRACT

Objective: Chronic watery diarrhoea is a classical symptom of collagenous colitis (CC). However, in some cases, the typical histologic findings of CC can be found in patients without this symptom. In this study we have performed a follow up on patients with a confirmed histological diagnosis of CC without the typical symptom watery diarrhoea.

Patients and methods: A structured medical record follow-up was performed on the subgroup of patients without watery diarrhoea but diagnosed with the typical CC histologic appearance in a previous study of microscopic colitis.

Results: At follow up after a median time of 8 years (range: 0.33–12 years), five of these fifteen patients developed bowel symptoms but only two developed characteristic CC symptoms with watery diarrhoea.

Conclusion: The majority of patients without chronic watery diarrhoea at diagnosis remained free from this symptom during follow up and only in a few cases symptoms attributed to CC developed.

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Collagenous colitis; epidemiology; clinical course; bowel symptoms

Introduction

Frequent, watery diarrhoea is a classical symptom of collagenous colitis (CC). However, in some cases, the typical histologic appearance, thickened collagen layer of at least 10 μm together with signs of inflammation [1], can be found in patients without this symptom. This was described already in 1988 in three patients with constipation [2] and in a case report from 1993 after surgery for constipation [3]. In the ICURE cohort (the IBD Cohort Uppsala Region), we have identified incident cases of inflammatory bowel disease (IBD) and microscopic colitis (MC) in the Uppsala health care region during the years 2005-2009 [4–6]. We identified 272 cases of MC, 154 with CC and 118 with lymphocytic colitis (LC). In almost 10% (15/154), of the CC cases, the patients lacked the typical symptom, watery diarrhoea [5].

In our previous study [5] we found that a majority of the patients with CC had only one symptomatic episode of MC, and only 14% of the patients had chronic symptoms at follow-up after at least one year. This relatively benign clinical course is in line with a report from the European pro-MC collaboration presented as a poster at UEG 2018 (Poster number P0915, L.K. Munck et al, personal communication), where 69% of the CC patients (24/35) had mild or quiescent disease and only 9% of the patients had chronic symptoms after one year.

CC is in general a benign disease with low risk of complications and with no increased risk for i.e. colonic cancer, although symptomatic CC may seriously influence health related quality of life [7,8].

Little is known about the long term prognosis of the selected patient group with histological diagnosis of CC but without diarrhoea at diagnosis. In this report we have performed a follow up on patients with a confirmed histological diagnosis of CC but were lacking the typical symptom watery diarrhoea at the time of the index colonoscopy.

Patients and methods

We have performed a follow-up by scrutinising the medical records of 15 patients with collagenous colitis lacking watery diarrhoea at diagnosis. The indications for taking biopsies in these patients were weak or not clear in many cases. We checked the records after the index colonoscopy with regard to gastrointestinal symptoms, endoscopies and medication described both in hospital records and when available also in the primary care records. Please see Table 1 for demographics and the indication for colonoscopy.

Ethical considerations

The study was approved by the local Ethics Committee at Uppsala University.

Results

Of the 15 patients lacking chronic watery diarrhoea at diagnose, nine were women; the median age was 73 years...
Median follow-up was 8.2 years (range 0.3–12.0) years. The majority of the patients did not develop any classical symptoms of CC. There were in all five patients who developed gastrointestinal symptoms and were treated with budesonide or prednisolone. Two patients presented with watery diarrhoea after 3 and 10 years, respectively. Moreover, one patient had an atypical clinical picture with mainly abdominal pain and disturbed bowel movements but as a result of the histopathology report was treated with budesonide and responded well to long-term treatment. In addition, one patient had abdominal pain and obstipation and was treated with prednisolone and later budesonide with good effect. Finally, one patient with only 4 months of follow-up received short term prednisolone and later budesonide.

Eight patients died during the follow-up time, most of them at high age and of cardiovascular disease except one death due to malignancy (cervical carcinoma). No death was related to gastrointestinal disease.

Four patients had colonoscopies during follow-up. New biopsies were taken in one of these cases and the histology had returned to normal.

As most patients had no or only minor GI symptoms there was no celiac diagnostic screening except in the cases with IBS like symptoms where 4/6 patients was investigated for celiac disease. In two cases these the result showed no signs of celiac disease (one with a normal duodenal biopsy and one with negative serology). One patient in whom the index colonoscopy was performed due to abdominal pain and obstipation had a previously diagnosed, but not fully resolved celiac disease due to low compliance. Furthermore, one patient developed iron and folate deficiency nine years after index colonoscopy and a celiac disease was diagnosed. The patient responded well to gluten free diet and had a normal duodenal biopsy after 18 months of gluten free diet a few weeks after she presented with frequent watery diarrhoea 10 years after the index colonoscopy.

Please see Table 1 for follow-up time and symptoms.

For the seven patients that had anaemia or bleed in stool (positive F-Hb) as indication for colonoscopy there were various findings in the colonoscopy report. Three patients had colonic polyps (adenomas), two had unspecific redness and frailty of the colonic surface, one had upper GI bleeding and in one patient the source of bleeding was not found. Two patients had obstipation as primary indication for index colonoscopy. One of these patients had a polyp and in the second case there was no particular finding.

### Discussion

The main finding in this study was that the majority of the patients diagnosed with typical histological findings of CC but without chronic watery diarrhoea, did not develop symptoms during the follow up. However, in a few cases gastrointestinal symptoms developed, but only two of these patients displayed classical CC symptoms with watery diarrhoea.

Although typical histological findings of CC in patients with constipation (3/21) was described as early as in 1988 [2], and in 1993 this was described in a patient with severe constipation requiring surgery [3] not much attention has been paid to this observation during the following years. On the contrary, chronic watery diarrhoea has been considered a prerequisite for the diagnosis of CC. We believe that this is a mistake that could blur the discussion regarding pathophysiology and understanding of the symptoms of the disease.

CC is not an unusual condition and in a Danish epidemiology study, the incidence increased during a study period of 10 years (2002–2011) from 2.9/105/year to 14.9/105/year.
Other reports as well, have found increasing incidence for example, in Olmstead county, Pardi et al. [10] reported an increased incidence between 1985 and 2001 but in a more recent report from the same area Gentile et al. [11] found that the incidence has stabilised at a CC incidence of 9.1/10^5/year. In our previous report the incidence was 7.1/10^5/year for CC [5].

In our previous report we found that approximately 10% (15/144) of the CC patients lacked the classical symptoms but displayed the typical histological picture of CC.

In a recent epidemiological study on microscopic colitis from Northern Ireland, 28 percent of the CC patients did not receive any treatment. This indicates no or very mild symptoms although the details on presenting symptoms was not collected in this Irish study [12].

Further, in a study from Finland [13] including 30 CC patients, 10% of the CC patients had anaemia or faecal blood as main or additional indication for colonoscopy and only 70% had watery diarrhoea at time of the colonoscopy. As in our study the diagnosis of CC was made based on the historical criteria.

The pathogenesis of the diarrhoea in CC is not fully clarified but as discussed in a recent review by Gentile and Yen [14], several potential mechanisms could be of importance, such as mucosal permeability, polymorphism of a serotonin reuptake transporter, bile acid malabsorption and inflammatory mediators in lamina propria.

Already in 1985, Bo-Linn et al. [15] showed with a bowel perfusion model that patients with microscopic colitis had reduced colonic absorption of water and electrolytes and proposed reduced active sodium and chloride absorption, inhibition of chloride/bicarbonate exchange, and decreased passive permeability of the mucosa as potential pathophysiological mechanism for diarrhoea.

In 1992, a group in Dallas investigated multiple serial biopsies in 24 patients with MC and 9 controls and found that stool weight correlated with lamina propria cellularity but not with thickness of the collagen layer [16]. Burgel et al. reported reduced Na and Cl absorption as the predominant diarrhoeal mechanism in collagenous colitis together with a secretory component of active electrogenic chloride secretion. The subepithelial collagenous band was described as a cofactor in the diffusion barrier [17].

Münch et al. found that bacterial uptake was increased both in patients with symptomatic CC and in patients in clinical remission after budesonide treatment indicating an underlying mucosal barrier defect [18]. Further, the same group found that the mucosal barrier effect led to an increased vulnerability to bile acids even in low levels leading to increase of bacterial uptake through the colonic epithelium in CC patients [19].

In most epidemiological studies of CC there has been a female preponderance. For example, in a study from Olmstead county, Minnesota 87% of the 46 CC patients was female [20]. A pronounced female dominance of 7:1 in CC was shown by Tysk et al. from Örebro, Sweden [7]. In our ICURE population the female: male ratio was 4.3:1 for CC [5].

However, in this limited patient group of patients lacking the classical CC symptoms at diagnoses, the female/male ratio was 1.5:1. This is an interesting observation although this finding should be interpreted with caution because of the small sample size.

During follow-up five of the 15 patients were treated with steroids, four of them with budesonide with good effect even though not all these patients had the classical CC symptoms.

The indication for the index colonoscopy, i.e. bleeding or IBS-like symptoms seemed to have no influence on the clinical course of the patients.

A weakness of the study is that the patients are not followed through protocol specific intervals with questions regarding their symptoms but the data are collected through scrutinising of medical records. The advantage of this study is that this is a prospectively collected population based patient cohort resulting in a high external validity.

In conclusion, we found that the majority of CC patients lacking the cardinal symptoms of frequent watery diarrhoea at time of diagnosis did not develop these symptoms during the follow-up. Furthermore, this observation points to the importance of looking beyond the collagen layer in search for the mechanism of diarrhoea.

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Daniel Sjöberg received speaker honoraria from Tillotts Pharma AB. The remaining authors have no competing interests to declare.

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