

Colonoscopic findings in coeliac disease on a gluten-free diet

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ABSTRACT

Background: to date, there are few data on colonoscopic findings in patients with coeliac disease, and most of these obtained in patients with iron deficiency anaemia.

Aims: we assessed colonoscopic findings in unselected patients with coeliac disease, since there are no studies available also considering morphological aspects, and there is literature suggestion of increased prevalence of colorectal tumours.

Material and methods: colonoscopies with multiple biopsies were retrospectively analyzed in 42 coeliac disease patients on gluten-free diet above age 40; 16 had clinical or laboratory features of iron deficiency anaemia. Mucosal biopsies were evaluated for the presence of intraepithelial lymphocytes and of mucosal eosinophils, in addition to conventional histologic assessment, and compared with those obtained in 15 controls.

Results: macroscopic abnormalities (polyps, diverticula, inflammatory changes) were found in 26% of patients. Microscopic abnormalities (lymphocytic colitis, melanosis coli, rectal histiocytosis) were found in 36% of patients. None of these findings was found in controls. Coeliac disease patients had significantly higher eosinophil score than controls in the right colon, whereas this was not significantly different between groups in the left colon.

Conclusions: colonoscopic findings in coeliac disease on gluten-free diet may reveal significant findings, even in patients without iron deficiency anaemia. There is the need of further studies in larger cohorts of patients to establish whether colonoscopy in these patients may be clinically useful.

Key words: Coeliac disease. Colitis. Colonoscopy.

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INTRODUCTION

It is a common belief that colonoscopy should be considered in adult patients with coeliac disease who present with iron deficiency anaemia or persisting diarrhoea while on a gluten-free diet (1), since coeliac disease is often pauci- or asymptomatic, and it is not infrequent to see patients diagnosed after age 40 (2). In fact, several patients may have microscopic colitis (collagenous or lymphocytic colitis), sometimes limited to the right colon (3), and there is a high prevalence of colorectal neoplasia among older patients with coeliac disease who present with iron deficiency or altered bowel habit (4).

Since as far as we know there are no specific studies investigating colonoscopic and morphological aspects in patients with coeliac disease on gluten-free diet, the purpose of this study was that of evaluating such findings in a retrospective series of patients undergoing colonoscopy.

PATIENTS AND METHODS

We retrospectively evaluated all colonoscopies carried out in adult patients with coeliac disease on gluten-free diet above age 40 in the period January 2008-September 2009. Apart from obvious macroscopic pathology, multiple biopsies throughout the colon with a minimum of two biopsies for each segment were taken from the right colon (ascending to the distal transverse), the left colon (splenic flexure to the rectosigmoid junction), and the rectum, even when the mucosa appeared macroscopically normal, as previously described (5).

All biopsy samples were oriented on acetate filters. Histological sections were processed, stained with H&E for conventional histology and immunostained with CD3 for evaluation of T lymphocytes. We considered diagnostic for lymphocytic colitis the number of 30/100 epithelial cells in the superficial epithelium of colonic mucosa (6). The scoring for eosinophil infiltration per x40 field was adapted from previously described criteria (5,7): 0 = occasional

eosinophils (average: 1-3); 1 = mildly increased eosinophils (average: 4-8); 2 = moderately increased eosinophils (average: 9-15); 3 = markedly increased eosinophils (average: > 15); 4 = severely increased eosinophils (average: > 30). Eosinophil score was calculated separately for the right and the left colon.

Mucosal biopsies were compared with those obtained from 15 subjects, 8 men, 7 women, aged 47 (range 40-63) years, without gastrointestinal diseases, 10 undergoing colonoscopy due to unspecific symptoms to rule out irritable bowel syndrome (8) and 5 for colorectal cancer screening, all with negative examinations of the colon. Bowel preparation was the same for both patients and controls, and it was carried out by drinking 4 L of a polyethylene glycol solution the day before the procedure.

The sections were interspersed and coded in a Pathology unit, and read in blind in a different Pathology unit by one investigator unaware of the endoscopic diagnosis.

Ethical considerations

Dealing with a retrospective study, no individual patient identification was involved and no study-driven clinical intervention was performed; therefore no ethical approval was necessary.

Statistical analysis

Eosinophil scores in the right and left colon were compared in the two groups by nonparametric means, using the Mann-Whitney U test. Values of $p < 0.05$ were chosen for rejection of the null hypothesis. Data are expressed as mean \pm SD.

RESULTS

In the 20-month observation period data from 48 adult coeliac disease patients over 40 years old (all on gluten-free diet) were identified and retrieved. Of these, 42 (87.5%) (29 females and 13 males, mean age 50 ± 1 yrs, range 40-71) had multiple biopsies available for review according to the above criteria. Colonoscopy (carried out under conscious sedation with midazolam, 3-5 mg intravenously) was done on average 5 ± 0.6 yrs (range 1-18) after coeliac disease was diagnosed (with all patients starting a gluten-free immediately after the diagnosis), and the reason was laboratory evidence of iron deficiency anaemia in sixteen patients (38%) and sporadic diarrhea/constipation or abdominal discomfort in the remaining. The duration of colonoscopy with multiple biopsy sampling required 20-40 minutes for each patient.

Table I shows colonoscopic and histologic findings found in these patients. Overall, macroscopic abnormalities were found in 11 (26%) patients: 7 adenomatous

Table I. Colonoscopic findings in CD patients

Nº	Age (years)	Macroscopic findings	Histologic findings
1	56	None	None
2	59	Sessile polyp of hepatic flexure	2 tubulovillous adenoma (LGD)
3	60	Sigmoid diverticula	RH
4	60	Multiple rectal polyps	Hyperplastic polyps, RH
5	55	None	RH
6	47	None	MC, LC
7	40	None	RH
8	71	None	None
9	57	Sigmoid diverticula	LC
10	49	None	MC
11	55	Multiple rectal polyps	Hyperplastic polyps, RH
12	53	None	MC, RH
13	45	Sigmoid diverticula	MC
14	67	None	MC, RH
15	40	None	RH
16	44	None	None
17	51	None	None
18	55	Sigmoid pedunculated polyp	2 tubular adenoma (LGD), RH
19	40	None	None
20	55	Sigmoid polyp	Tubular adenoma (LGD), RH
21	58	None	MC
22	44	None	MC, RH
23	42	None	MC
24	54	None	MC
25	40	None	MC, RH
26	45	None	None
27	40	None	RH
28	54	Sigmoid polyp	Tubular adenoma (LGD), MC
29	40	None	RH
30	47	Transverse colon polyp	Inflammatory polyp, RH
31	63	Ascending colon polyp	Tubular adenoma (LGD)
32	49	None	RH
33	41	None	RH
34	40	None	None
35	54	None	None
36	41	None	MC, RH
37	62	Cecal polyp	Hyperplastic polyp, RH
38	44	None	LC, MC
39	53	None	None
40	40	Mild left-side colitis	Ulcerative colitis
41	40	Mild pancolitis	Ulcerative colitis
42	47	None	None

LC: lymphocytic colitis; LGD: low-grade dysplasia; MC: melanosis coli; RH: rectal histiocytosis.

polyps 1-2 cm diameter (all endoscopically removed; histological examination revealed low-grade dysplasia in all) in 5 patients; sigmoid diverticular disease in 3 patients, multiple small rectal (hyperplastic) polyps in 2 patients, and inflammatory (mild ulcerative colitis) findings in 2 patients.

Microscopic findings (Fig. 1): two patients (4.7%) had histological features of lymphocytic colitis. Other findings were represented by the presence of histologically-detected melanosis coli in 13 (31%) patients and of intense rectal histiocytosis –defined as the presence of foamy histiocytes readily observed at low-power magnification (40 \times) and positive to CD68, the marker judged to have the better results for their confirmation (9)–, with small branching of muscular fibers from *muscularis mu-*

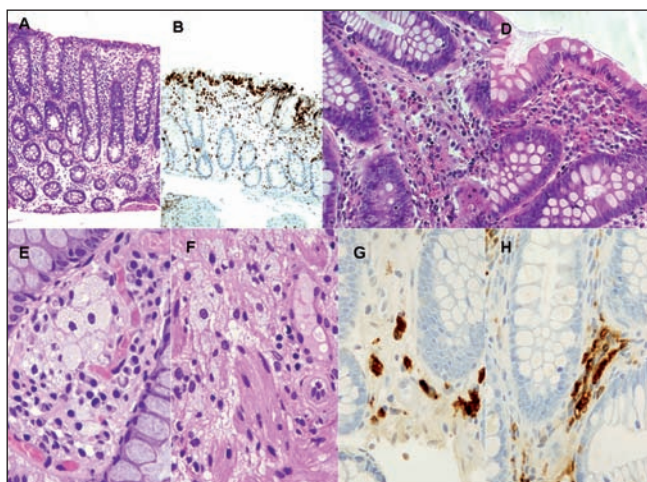


Fig. 1. A. Lymphocytic colitis. H&E, original magnification x20. B. Lymphocytic colitis. CD3, original magnification x10. Note the pathological increase of intraepithelial lymphocytes in both A and B. C and D. Increased number of eosinophils in the lamina propria of the right colon of two celiac patients. H&E, original magnification x40. E and F. Presence of foamy histiocytes within the rectal mucosa of two celiac patients. H&E, original magnification x100. G and H. Rectal histiocytes in the rectal mucosa, showing CD68 positivity. Original magnification x100.

cosae penetrating the lamina propria. Interestingly, these findings were related to decrease bowel movements (with some patients reporting straining at stools when questioned) after starting a gluten-free diet. None of the above findings was found in controls.

Compared to controls, coeliac disease patients had significantly higher eosinophil score in the right colon -1.7 ± 0.4 (range 1-2) vs. 2.2 ± 0.9 (range 0-4), $p = 0.039$ -, whereas no differences were found in the left colon -1.4 ± 0.2 (range 1-2) vs. 1.6 ± 1 (0-3), $p = 0.55$ -.

DISCUSSION

Why should we perform a colonoscopy in a patient with known or suspected coeliac disease? There is presently enough evidence to suggest that in patients with iron deficiency anaemia colonoscopy is useful to detect occult coeliac disease (1,10); also, colonoscopy is to be considered in older patients with coeliac disease who present with iron deficiency anaemia or abnormal bowel habit, due to the high prevalence of colorectal tumours (3) and to the fact that occult gastrointestinal bleeding can be detected in about half of patients with coeliac disease (11).

On the other hand the relationship between coeliac disease and microscopic (including lymphocytic and collagenous) colitis (12,13) should prompt to carry out colonoscopy in the presence of suspicious symptoms.

Here we report our experience on colonoscopic findings in patients with coeliac disease on gluten-free diet; in addition, data were obtained on colonic histopathologic findings, especially on the number of eosinophils. Of

course, this study has limitations, being a retrospective investigation, and due to the relatively small cohort of patients and controls we obtained. However, we feel that some observations we made could be of interest.

Concerning macroscopic abnormalities, adenoma detection rate (12%) was somewhat lower than observed in screening colonoscopy programs (14,15), and no malignancies were detected (although this may be due to the group being quite young and the limited number of subjects investigated) whereas the occurrence of diverticular disease in 7% of patients is likely to be expected in routine colonoscopies carried out in a relatively young age group (16). Also, the fact that 2 patients had ulcerative colitis is not surprising, since there is evidence that prevalence of inflammatory bowel diseases in coeliac disease is increased 10-fold compared with that in controls (17). On the other hand, no cases of collagenous colitis and only two cases of lymphocytic colitis were found in this series, whereas these entities were found more frequently in other authors' experience (18).

One third of our patients had melanosis coli and rectal histiocytosis, two findings associated with constipation (9,19); indeed, and worth noting, all these patients developed mild to moderate constipation after starting a gluten-free diet. Interestingly, this fact was overlooked during the initial evaluation, and come to our attention only after specific questioning once histological results were available. A subsequent literature search confirmed that coeliac disease patients on gluten-free diet may, among other symptoms, do indeed become constipated (20,21), probably due to the composition of the diet itself.

How can we explain the increased number of eosinophils in our patients? The presence of eosinophils in the intestinal mucosa of patients with coeliac disease is a well established fact (22,23), and these cells actively participate in the mucosal challenge to gliadin of these patients (24-26). However, data on the colon are scarce, and mostly related to the use of nonsteroidal anti-inflammatory drugs (none of our patients had used them -or other drugs- in the three months before colonoscopy) (7,27) or to the presence of collagenous colitis (excluded in our series by the lack of a compatible clinical picture and the histological findings) (28,29). The fact that the increase of eosinophils was prevalent in the right compared to the left colon is also against the possibility of a reaction due to drug ingestion (where mucosal eosinophilia is constantly concentrated, with very high scores, in the left colonic segments) (5).

In conclusion, colonoscopic findings in coeliac disease on gluten-free diet may reveal interesting (and sometimes important) findings, even in patients without iron deficiency anaemia. Whether this fact may justify a systematic approach in all coeliac disease patients (taking into account that a substantial portion of these patients often present extra-intestinal or atypical symptoms) (30,31) remains to be established, and will need investigation of larger cohorts of patients in a prospective manner.

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