

The Yield of Mapping Biopsy from Apparent Endoscopically Normal Colon and Correlation with Symptoms

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ABSTRACT

AIM: There are controversies about the importance of biopsies of normal colonic mucosa in the investigation of patients with chronic lower gastrointestinal symptoms so the aim of our work to evaluate the clinical significance of mapping biopsy and its yield in patients with apparent endoscopically normal colon who is investigated for chronic complaint and to discover the prevalence of hidden diseases and its correlation with the symptomatology in our locality.

METHODS: 90 patients with normal colonoscopy were included. Multiple biopsies were taken during the colonoscopy and reviewed by the same pathologist. Cases were retrieved over a 12-month period. Histopathology results were correlated with relevant symptomatology and the data were analyzed.

RESULTS: 90 cases which were reported as endoscopically normal/near normal were selected. 70 of the 90 cases showed normal/near normal histology. Of the remaining 20 case with abnormal histology, 10 cases showed microscopic colitis, 3 cases showed lymphocytic colitis, 3 cases showed collagenous colitis, 3 cases showed drug induced colitis, and 1 case showed evidence of bilharzial colitis.

CONCLUSION: Pathological abnormalities in endoscopically normal colon were found in 22.2% of our cases and most frequently in those who presented with change in bowel habit (13/26, 50%). The diagnostic yields were very low in patients referred for other reasons (e.g. bright red rectal bleeding or iron deficiency anemia).

INTRODUCTION

Endoscopic colonic mapping biopsies are widely used as a diagnostic tool in investigation of inflammatory bowel pathology and represent a significant proportion of the workload of any gastrointestinal histopathology service. Mapping biopsy of the colon involves a series of multiple mucosal biopsies taken sequentially from proximal to distal^[1]. The role of biopsy in the endoscopically normal colorectum is an area of contention^[2].

Although it is firmly established that certain pathology, for example microscopic colitis and crohn's disease may occur in normal colonic mucosa by endoscopic examination. The reported rates of histological diagnoses made from seemingly normal mucosa vary widely between 3% and 32.1% in previously published studies^[3,1]. Exclusion of microscopic colitis is a common reason for mapping biopsies to be taken during an endoscopically normal sigmoidoscopy or colonoscopy^[4].

The Royal College of pathologists commented in their document histopathology and cytopathology of limited or no value that endoscopic biopsy of the normal colon should only be performed in patient in the correct clinical setting with a history of persistent watery diarrhea without blood^[5]. The British Society of Gastroenterology in association with the Joint Group in Gastrointestinal Endoscopy state in their document "Quality and Safety Indicators for endoscopy" that biopsies should be performed in 100% of individuals with persistent diarrhea^[6].

Microscopic colitis is regarded as a common cause of chronic watery diarrhea accounting for approximately 4%-13% of patients

presenting with this symptom. By definition, the colon appears normal or nearly normal on colonoscopy with set histopathological criteria required for the diagnosis on mucosal biopsy^[7].

There are only few reports of microscopic colitis from developing countries. A study in Peru, with high prevalence of infectious gastroenteritis, revealed microscopic colitis in 40% of patients with chronic watery non-bloody diarrhea, more commonly of the lymphocytic type^[8]. Another study in Tunis revealed microscopic colitis in 29.3% of patients with chronic watery non-bloody diarrhea^[9].

This study was designed to detect the rates of histological diagnoses made from seemingly normal mucosa in our locality sharkia governorate and to determine the prognosis as well as necessity of the further work up in such cases.

METHODS

All patients aged 15 to 75 years old presented with chronic diarrhea, chronic abdominal pain, hematochezia, and/or anemia between September 2012 and end of December 2013. All patients were referred to gastroenterology unit of Internal medicine department, faculty of medicine, Zagazig University, Egypt. Complaining of any one or combination of the mentioned complaints and a normal total colonoscopy were the criteria for the patients to be enrolled. The exclusion criteria were past medical history of any gastrointestinal disorders which may present with the previous mentioned complaints including diverticulosis, vascular abnormalities, radiation-induced pathologies, inflammatory bowel disease, neoplasm, and other anorectal disorders such as haemorrhoid, ulcer as well as any macroscopic colonoscopic findings which could produce these complaints. Ninety patients with normal colonoscopy were included in the study.

All patients were firstly evaluated in the first visit; a questionnaire was filled for each patient during a face-to-face interview about the full history of their symptoms, their bowel habit, and their past medical history of any gastrointestinal and non-gastrointestinal disorders. Before the procedure, complete bowel preparation was performed for all patients. At least twelve to fifteen hours prior to procedure, patients were instructed to drink 280 g of polyethylene glycol powder (PIDROLAX, Sepidag Pharmacologic Company) solved in four liter of water in fifteen minutes intervals. All colonoscopies were performed using an Olympus Q230 or Q240 videocolonoscope (Olympus Co., Tokyo, Japan), by a single expert gastroenterologist to eliminate any person-to-person variability. The completeness of colonoscopy was assured by visualization of terminal ileum. Ninety patients with normal or near normal colonoscopy were selected. During colonoscopy two biopsies were taken from terminal ileum and all segments of the colon. The mean numbers of biopsy samples from rectosigmoid, descending, transverse, ascending colon were 3 from each segment (range 1-6 tissue fragments). They were immediately placed in separate vials with 10% formalin, processed conventionally in paraffin blocks and cut into 5 micrometer thick unstained sections. The slides were stained with Hematoxylin and Eosin (H and E) and Masson's trichrome dyes.

Histological criteria

Histological diagnosis of lymphocytic colitis was confirmed with ≥ 20 intraepithelial lymphocyte count per 100 surface epithelial cells, with normal being < 5 . In addition, a mixed inflammatory infiltrate in the lamina propria that consisted of lymphocytes and plasma cells with surface epithelial damage was noted^[10]. Diagnosis of collagenous colitis was established with a subepithelial collagen layer reaching or exceeding $10 \mu\text{m}$ ^[11].

This study was approved by constituted Ethics Committee of the Zagazig University, Faculty of medicine within which the work was undertaken. It also conformed to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2000).

Statistical analysis

Data were expressed as proportions. Results were compared by using the Chi-Square test. SPSS software version 15 was used for statistical analyses and 95% confidence intervals were computed and statistical significance was defined as $P < 0.05$.

RESULTS

The age range of the 90 patients was 15 to 75 years, with a mean age of 38.6 years. Of them, 31 (34.5%) patients were female and 59 (65.5%) patients were male. The chief complaints of all 90 patients are shown in table 1, which was intermittent in 80 (88.9%) patients.

Table 1 Chief complaints of the studied patients at recruitment.

Complaint	Number of patients	Percentage
Chronic diarrhea	20	22.2%
Chronic constipation	9	10%
Chronic abdominal pain	31	34.4%
Rectal bleeding	23	25.6%
Change in bowel habit with rectal bleeding	1	1.1%
Change in bowel habit with abdominal pain	5	5.5%
Iron deficiency anemia	1	1.1%
Total = 90		

Colonoscopy results were normal in 79 (87.8%) and were near normal with mild non-specific changes (erythema and edema) in 11 (12.2%) patients..

Of the 90 patients, 70 (77.8%) presented normal histology. Of the remaining 20 (22.2%) patients with abnormal histology, 10 (11.1%) showed microscopic colitis not otherwise specified (Figure 1), 3 (3.35%) presented typical histological features of lymphocytic colitis (Figure 2), 3 (3.35%) patients showed collagenous colitis (Figure 3), 3 (3.35%) patients showed drug induced colitis (Figure 4), and only one (1.1%) patient showed evidence of bilharzial colitis (Table 2).

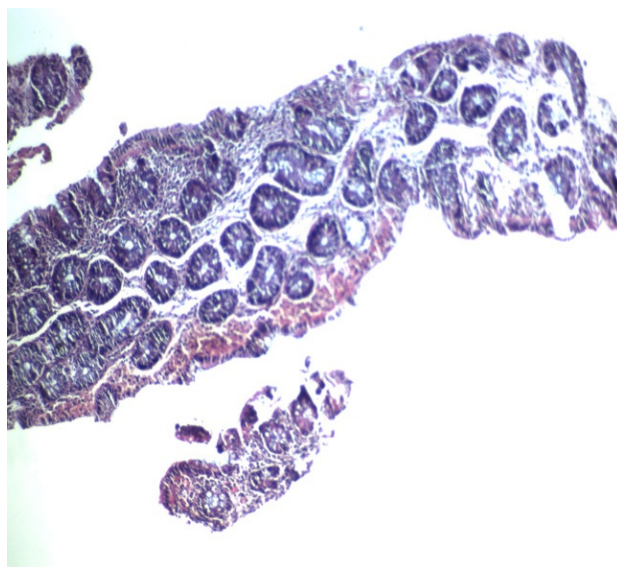


Figure 1 A case of microscopic colitis showing epithelial damage with mild aggregates of inflammatory cells in the connective tissue (H and E stain).

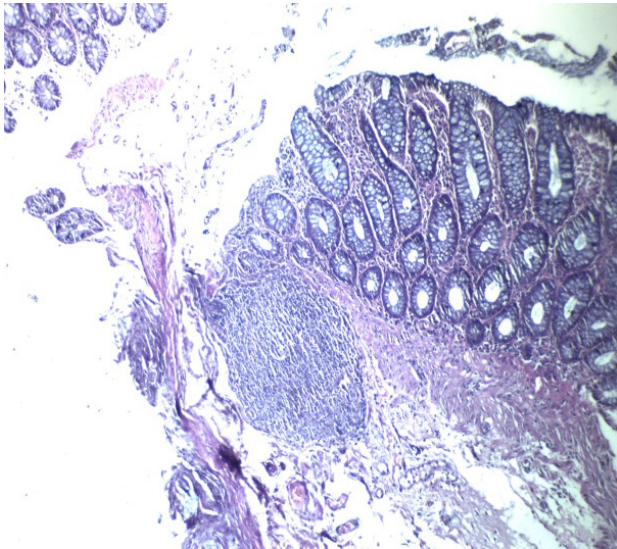


Figure 2 A case of lymphocytic colitis showing round aggregates of lymphocytic cells in the lamina propria beneath the mucous glands (H and E stain).

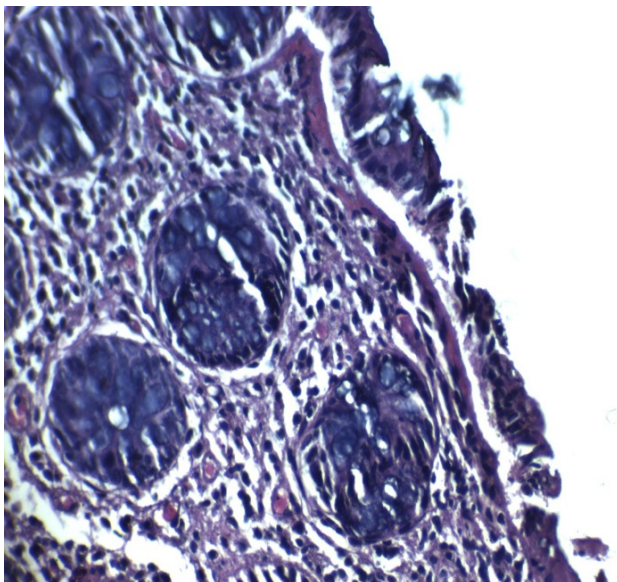


Figure 3 A case of collagenous colitis showing a band of collagen beneath the surface epithelium (H and E stain).

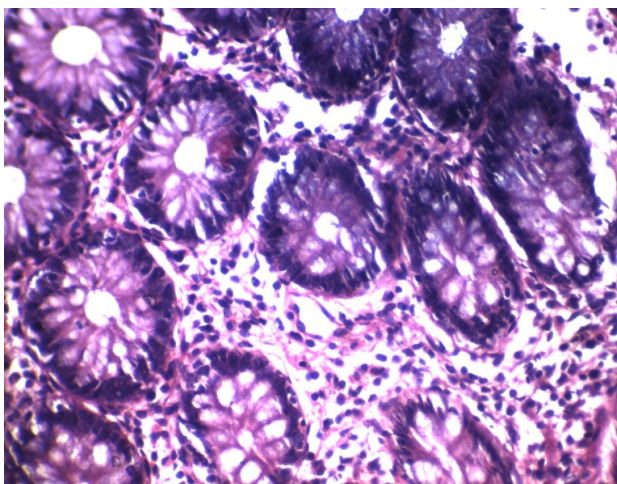


Figure 4 A case of drug induced colitis characterized by large number of eosinophils in between the mucous glands (H and E stain).

Table 2 Colonic histopathological findings.

Histopathologic diagnosis	Number of patients	Percentage
Normal	70	77.8%
Abnormal	20	22.2%
Microscopic colitis	10	11.1%
Lymphocytic colitis	3	3.35%
Collagenous colitis	3	3.35%
Drug induced colitis	3	3.35%
Bilharzial colitis	1	1.1%
Total = 90		

Regarding the symptomatology, 11 of the 20 patients (55%) who complaining from chronic diarrhea had abnormal histopathological findings (6 cases microscopic colitis, 1 case lymphocytic colitis, 1 case collagenous colitis, 1 case hyperplastic polyp, and 2 cases drug induced colitis); 5 of the 31 patients (16.1%) who complaining from chronic abdominal pain only had abnormal histopathological findings (2 cases microscopic colitis, 2 cases collagenous colitis, and 1 cases drug induced colitis); 2 of the 23 patients (8.7%) who complaining from rectal bleeding had abnormal histopathological findings (2 cases microscopic colitis); 1 of 1 patient (100%) who complaining from change in bowel habit and rectal bleeding had abnormal histopathological findings (1 case lymphocytic colitis); and 1 of the 5 patients (20%) who complaining from change in bowel habit and abdominal pain had abnormal histopathological findings (1 case lymphocytic colitis). All patients with chronic constipation and iron deficiency anemia had normal histopathological findings (Table 3).

Table 3 Relation between histopathological findings and symptomatology.

Complaint (total number=90 patients)	Number of abnormal finding	Number of normal finding	χ^2	P value
Chronic diarrhea (20 patients)	11	9	9.9	0.002
Chronic abdominal pain only (31 patients)	5	26	1.23	0.26
Rectal bleeding (23 patients)	2	21	0.86	0.35
Change in bowel habit and rectal bleeding (1 patient)	1	0	0.9	0.018
Change in bowel habit and abdominal pain (5 patients)	1	4	0.9	0.018
Chronic constipation (9 patients)	0	9	1.02	0.31
Iron deficiency anemia (1 patient)	0	1	1.02	0.31

DISCUSSION

There are controversies about taking routine mucosal biopsy when the gross colonoscopic findings are normal. Flexible sigmoidoscopy or colonoscopy is often used by many physicians to find the organic cause of lower GIT symptoms and some gastroenterologists perform routine mucosal biopsies to exclude organic causes of lower GIT symptoms as chronic diarrhea that can only be diagnosed microscopically even when the endoscopic findings are normal. Diseases that cause diarrhea when the endoscopic findings are normal or non-specific include collagenous colitis, lymphocytic colitis and eosinophilic enterocolitis. Melanosis coli is a sign of laxative abuse may be seen only microscopically. Finding these histological abnormalities in grossly normal colonic mucosa may alter the therapeutic decisions by implicating the use of immunosuppressive drugs such as corticosteroid or the need for close clinical follow up^[12]. Some suggest colonic biopsies should be taken routinely^[13] while others argue about the cost-effectiveness of the procedure^[2].

Chronic diarrhea, reported by 4-5% of individuals of a Western

population, is a common cause for consulting a physician in general practice or internal medicine and for referral to a gastroenterologist^[14]. In the literature, the percentage of patients with diarrhea in whom a histological diagnosis could be made despite a normal endoscopy ranges from 15 to 40%^[15].

This study confirmed the established view that pathological changes can be detected microscopically in the setting of endoscopically normal mucosa. However, the diagnostic yield in our cohort was small (11.1 %) and was lower than that reported in much of the literature^[1]. The biopsies from 70 patients (77.8 %) out of 90 endoscopically normal or near normal cases which was studied, showed normal or near normal histological appearances and the remaining 20 (22.2%) patients was found with abnormal histology.

Our study is showing the relation between symptoms and histological abnormalities with significant abnormalities in chronic watery diarrhea ($p=0.002$), also significant abnormalities in change in bowel habit with abdominal pain ($p=0.018$), and change in bowel habit with rectal bleeding ($p=0.018$). There is no significant abnormalities in chronic constipation only ($p=0.31$), abdominal pain only ($p=0.26$), rectal bleeding only ($p=0.35$) and patients under investigations for iron deficiency anemia ($p=0.31$).

The incidence of microscopic colitis in patients with chronic watery diarrhea in this study was 40% which was similar to the higher prevalence rate reported in another study was done in Egypt which found the prevalence rate reach to 50%^[16] and also in other developed countries like Tunis 29.3%^[9] and Peru 40%^[8].

Many studies deny the usefulness of a routine mucosal biopsy. MacIntosh *et al*^[17] performed sigmoidoscopic biopsies on 134 patients with non-specific lower gastrointestinal symptoms and reported that they did not find any cases of collagenous colitis or lymphocytic colitis. Since the symptoms of the majority of patients with collagenous colitis and lymphocytic colitis manifest as chronic watery diarrhea, they might have included cases that are unlikely to be collagenous colitis or lymphocytic colitis. Only rectal biopsies were performed in their study, which suggest that the cases that are confined to the right side of the colon may have been missed.

Marshall *et al*^[2] have performed mucosal biopsies from normal looking mucosa obtained from 111 chronic diarrhea patients. They included all patients who had a change in their bowel habits, their data included one case of possible collagenous colitis and 13 (11.7%) cases that showed some features of lymphocytic colitis of which the clinical significance was denied by the authors. They thought that these cases should not be considered as trivial or non-specific findings.

Lee *et al*^[12] were able to find clinically significant histological abnormalities, findings that could alter the therapeutic decisions in 7.6% of patients (9/118); two cases of collagenous colitis, one case of lymphocytic colitis, one case of eosinophilic enterocolitis, one case of ulcerative colitis and four cases of melanosis coli.

Elliot *et al*^[18] studied 308 patients with gastrointestinal complaints as chronic watery diarrhea, abdominal pain and other symptoms and normal colonoscopies. They found that there were 30/308 (9.7%) endoscopically normal cases showed pathological abnormalities. 9/308 (2.9%) cases of microscopic colitis were detected and of the thirty case with pathological abnormalities, twenty (66.7%) case presented by change in the bowel habit.

There is variable guidance on the best approach to examination and sampling in patients with chronic diarrhea and a normal colonoscopy^[18]. However, full colonoscopy showed an increased diagnostic yield over flexible sigmoidoscopy because in some conditions, for example collagenous colitis, pathological changes

may be patchy or confined solely to the proximal colon^[19]. Recommendations on the numbers of biopsies to be taken are limited; Marshall *et al*^[2] suggest six biopsies from throughout the colon in patients with chronic diarrhea should be sufficient.

Our study had also shown that in certain clearly defined clinical situations, the likelihood of identifying significant pathological changes from a series of mapping biopsies of endoscopically normal colonic mucosa is very low. For example, biopsies taken from patients presenting with isolated chronic constipation, those being investigated solely for iron deficiency anemia, yielded no pathological abnormalities when the colonoscopic appearances were recorded as normal.

Pathologists continue to report considerable numbers of histologically normal colonic mapping biopsy series from patients with endoscopically normal colonic mucosa and a wide range of non-specific symptoms. Preparing and examining these sections is labor intensive, and time consuming for both laboratory staff and pathologists. After histopathological processing, a colonic mapping biopsy series of six to eight mucosal samples optimally produces slides with between 8 and 10 individual pieces of tissue for microscopic examination^[18].

In this study, we found that the majority (86.7%) of the biopsies with pathological abnormalities came from patients who presented with chronic watery non-bloody diarrhea, change in bowel habit and abdominal pain and change in bowel habit and rectal bleeding.

If, in this study cohort, we had only received biopsies from patients with normal colonoscopies who had presented with change in bowel habit (as an isolated symptom or in conjunction with other symptoms), we would have reduced the biopsy rate from 90 to 81 (a 10 % reduction).

This reduction of 10% is considered to be a conservative estimate. We believe that with more stringent criteria for selecting patients referred with change in bowel habit (i.e., restricting biopsy to those with persistent watery diarrhea); biopsy rates could be reduced still further. Currently, no quantitative parameters on the frequency or circumstances of any change in bowel habit are defined in the small amount of existing guidance on biopsy of the endoscopically normal colon, despite this being a difficult and often very subjective area on which an accurate clinical history could be obtained^[5]. Specific criteria would help to clarify patient symptoms and would further aid endoscopists in more effective selection of the most appropriate patients for biopsy.

CONCLUSION

This study confirms the established view that pathological changes can be detected microscopically in the setting of endoscopically normal mucosa. We also had confirmed that microscopic pathological abnormalities were detected most frequently in patients presenting with change in bowel habit. Biopsy of an endoscopically normal colon is unlikely to yield any diagnostically useful information and is not encouraged as routine in patients with constipation, abdominal pain, iron efficiency anemia, and slight non-recurrent bleeding.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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