



Clinicopathological Spectrum of Chronic Non-Bloody Diarrhoea: Diagnostic Yield of Colonoscopy and Histopathological Evaluation.

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Abstract

Background: Chronic non-bloody diarrhoea has a broad differential diagnosis, and the colonic mucosa frequently appears normal at colonoscopy. The diagnostic yield of colonoscopy with mucosal biopsy, and its overlap with a symptom-based diagnosis of diarrhoea-predominant irritable bowel syndrome (IBS-D), remains incompletely defined.

Aim: To describe the clinical, colonoscopic and histopathological spectrum of chronic non-bloody diarrhoea and to quantify the diagnostic yield of colonoscopy and histopathological evaluation. **Methods:** This cross-sectional observational study included 43 adults with chronic watery, non-bloody diarrhoea who underwent colonoscopy with mucosal biopsy at the Department of Medical Gastroenterology in Sri Siddhartha Medical College, Tumkur. Clinical features, laboratory parameters, colonoscopic findings and histological findings were recorded. Patients were classified according to the Rome III criteria for IBS-D. Proportions are reported with exact 95% confidence intervals, and groups were compared using Fisher's exact test. **Results:** The mean age was 44.9 ± 14.8 years and 26 patients (60.5%) were female. Colonoscopy was macroscopically normal in 38 patients (88.4%). Histology was normal in 18 (41.9%), showed nonspecific colitis in 14 (32.6%), lymphocytic colitis in 6 (14.0%), eosinophilic colitis in 2 (4.7%), and ulcerative colitis, Crohn's disease and intestinal tuberculosis in 1 patient each (2.3%). A specific histological diagnosis was established in 11 patients (25.6%; 95% CI 13.5–41.2%). Twenty patients (46.5%) fulfilled Rome III criteria for IBS-D; 14 of them (70.0%) had a histological abnormality, including lymphocytic colitis in 4 (20.0%). Patients with lymphocytic colitis were predominantly female (66.7%) and had nocturnal diarrhoea (83.3%); their mean age was 51.5 years. **Conclusion:** Colonoscopy was macroscopically normal in nearly nine out of ten patients, yet histology identified an abnormality in 58.1% and a specific diagnosis in 25.6%.

Keywords: chronic diarrhoea; colonoscopy; histopathology; microscopic colitis; lymphocytic colitis; irritable bowel syndrome.



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INTRODUCTION

Chronic diarrhoea, usually defined as loose or watery stools persisting for more than four weeks, is a common presentation to gastroenterology services and carries a wide differential that spans functional, inflammatory, infective, neoplastic, malabsorptive and drug-related causes [1,2]. Because history and examination alone rarely distinguish these causes reliably, ileocolonoscopy is a standard step in the evaluation of patients whose initial investigations are unrevealing [2,3]. A recurring difficulty is that the colonic mucosa often appears normal in chronic non-bloody diarrhoea. Microscopic colitis, comprising lymphocytic and collagenous colitis, is the prototype of a condition that is diagnosed only on histology and accounts for a meaningful proportion of patients with chronic watery diarrhoea [4–6]. Current guidelines therefore advise that biopsies be taken from a macroscopically normal colon in this setting [2,5]. Other conditions, including eosinophilic colitis and early or limited inflammatory bowel disease, and in endemic regions intestinal tuberculosis, may likewise present with watery diarrhoea and subtle or absent endoscopic change.

The clinical picture of microscopic colitis overlaps with that of diarrhoea-predominant irritable bowel syndrome (IBS-D) as defined by the Rome criteria [7]. A meta-analysis has shown that microscopic colitis is found in a minority of patients with IBS-type symptoms [8], so a symptom-based diagnosis may delay recognition of a treatable condition if histology is not obtained. Local data on the yield of colonoscopy and biopsy in chronic non-bloody diarrhoea, and on how that yield relates to a clinical IBS-D label, are limited, although tertiary-centre experience of microscopic colitis in India has been described [12]. We therefore studied patients with chronic watery, non-bloody diarrhoea to (1) describe their clinical profile, (2) define the colonoscopic and histopathological spectrum, (3) estimate the diagnostic yield of colonoscopy and

histopathology, and (4) compare histological findings between patients who did and did not fulfil Rome III criteria for IBS-D.

MATERIALS AND METHODS

Study design and setting. This cross-sectional observational study was conducted in the Department of Medical Gastroenterology at Sri Siddhartha Medical College, Tumkur, between August 2025 and July 2026. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants before enrolment and before colonoscopy.

Participants. Consecutive adults aged ≥ 18 years who presented with chronic watery, non-bloody diarrhoea and were advised colonoscopy were included. Chronic diarrhoea was defined as the passage of loose or watery stools (Bristol Stool Form Scale type 6 or 7) on at least three occasions per day, or stool frequency above the patient's normal, persisting for more than four weeks [1,2]. Patients were excluded if they had visible blood in the stool; stool microscopy or culture positive for enteric pathogens, ova or cysts, or a positive *Clostridioides difficile* test; a known diagnosis of inflammatory bowel disease, coeliac disease or colorectal malignancy; previous bowel resection; a clear drug-related cause of diarrhoea (for example laxatives or recent antibiotics); HIV infection or other known immunosuppression; pregnancy; an uncorrected coagulopathy or other contraindication to colonoscopy and biopsy; an inadequate bowel preparation; or refusal of consent.

Clinical and laboratory assessment. A structured proforma recorded age, sex, duration of diarrhoea, nocturnal diarrhoea, abdominal pain, weight loss, fever, smoking status (current or past) and autoimmune disease. Haemoglobin, total leucocyte count, platelet count and erythrocyte sedimentation rate (ESR) were measured. Patients were classified as fulfilling or not fulfilling the Rome III criteria for IBS-D [7].

Colonoscopy and biopsy. Colonoscopy was performed after overnight fasting and bowel preparation with a split dose of 4 L polyethylene glycol electrolyte solution, under conscious sedation where required, by experienced gastroenterologists using a standard video colonoscope. The examination was extended to the caecum, identified by the ileocaecal valve and appendiceal orifice, with intubation of the terminal ileum where feasible. Mucosal findings (erythema, loss of vascular pattern, granularity, friability, erosions, ulcers, nodularity or polyps) were recorded during withdrawal. In keeping with guideline recommendations [2,5], at least two mucosal biopsies were taken from each of the right colon (caecum or ascending colon), transverse colon, left colon (descending or sigmoid colon) and rectum, and from the terminal ileum when intubated, irrespective of whether the mucosa appeared normal; any macroscopic lesion was additionally biopsied and submitted separately. Specimens were placed immediately in 10% neutral buffered formalin and labelled by site.

Histopathology. Specimens were processed routinely, embedded in paraffin, and 4- μ m sections were stained with haematoxylin and eosin; Masson trichrome staining was used to assess the subepithelial collagen band, and Ziehl–Neelsen staining was performed when granulomas were present. Slides were examined by experienced gastrointestinal pathologists who were aware of the biopsy site but blinded to the clinical diagnosis. Lymphocytic colitis was diagnosed by the standard histological criteria [9,10]: more than 20 intraepithelial lymphocytes per 100 surface epithelial cells, increased lamina propria chronic inflammatory cells, surface epithelial injury and preserved crypt architecture, with a subepithelial collagen band thinner than 10 μ m (a band of 10 μ m or more indicating collagenous colitis). Nonspecific colitis was defined as a mild to moderate increase in lamina propria lymphocytes and plasma cells, with or without focal cryptitis, that did not satisfy the criteria for any specific entity (no distortion of crypt architecture, intraepithelial lymphocytosis below the diagnostic threshold, no granulomas and no excess of eosinophils). Eosinophilic colitis was diagnosed when a prominent eosinophilic infiltrate of the lamina propria (above site-specific reference counts) was present after exclusion of parasitic infection and drug causes. Ulcerative colitis, Crohn's disease and intestinal tuberculosis were diagnosed on combined histological, endoscopic and clinical findings: ulcerative colitis by diffuse crypt architectural distortion with basal plasmacytosis and a continuous distribution; Crohn's disease by patchy or focal inflammation with or without non-caseating epithelioid granulomas; and intestinal tuberculosis by confluent or caseating granulomas, or acid-fast bacilli, supported by clinical and microbiological evidence.

Outcomes. The primary outcome was diagnostic yield, expressed as (i) the proportion of patients with a macroscopic abnormality at colonoscopy, (ii) the proportion with any histological abnormality, and (iii) the proportion with a specific histological diagnosis (lymphocytic colitis, eosinophilic colitis, ulcerative colitis, Crohn's disease or intestinal tuberculosis, i.e. excluding normal histology and nonspecific colitis). Secondary outcomes were the characteristics of patients with lymphocytic colitis and the histological findings in patients with and without IBS-D.

Statistical analysis. Continuous variables are presented as means $\pm$ standard deviations, and categorical variables as numbers and percentages. Exact (Clopper–Pearson) 95% confidence intervals were calculated for proportions. Groups were compared using Fisher's exact test. A two-sided P value < 0.05 was considered statistically significant.

RESULTS

Study population

Forty-three patients were included (mean age 44.9 ± 14.8 years; 17 men and 26 women, female-to-male ratio 1.5:1). All presented with watery diarrhoea of mean duration 11 ± 3.2 months. Abdominal pain was reported by 33 patients (76.7%), nocturnal diarrhoea by 17 (39.5%) and weight loss by 11 (25.6%); fever was uncommon (2 patients, 4.7%). Five patients (11.6%) were current or past smokers and three (7.0%) had an autoimmune disease. Baseline characteristics are shown in Table 1 and the age distribution in Table 2 and Figure 1; 20 patients (46.5%) were aged 41–60 years.

Table 1. Baseline characteristics of the study population (N = 43)

Parameter	Value
Age, years, mean $\pm$ SD	44.9 ± 14.8
Male, n (%)	17 (39.5)
Female, n (%)	26 (60.5)
Duration of diarrhoea (months), mean $\pm$ SD	11 ± 3.2
Watery diarrhoea, n (%)	43 (100)
Nocturnal diarrhoea, n (%)	17 (39.5)
Abdominal pain, n (%)	33 (76.7)
Weight loss, n (%)	11 (25.6)
Fever, n (%)	2 (4.7)
Smoking (present or past), n (%)	5 (11.6)
Autoimmune disease, n (%)	3 (7.0)
Haemoglobin, g/dL, mean $\pm$ SD	10.2 ± 3.6
Total leucocyte count, /mm ³ , mean $\pm$ SD	$6,726 \pm 2,030$
Platelet count, /mm ³ , mean $\pm$ SD	$226,543 \pm 64,000$
ESR, mm/hour, mean $\pm$ SD	34 ± 12

SD, standard deviation; ESR, erythrocyte sedimentation rate.

Table 2. Age distribution (N = 43)

Age group (years)	n	%
18–30	9	20.9
31–40	9	20.9
41–50	10	23.3
51–60	10	23.3
>60	5	11.6

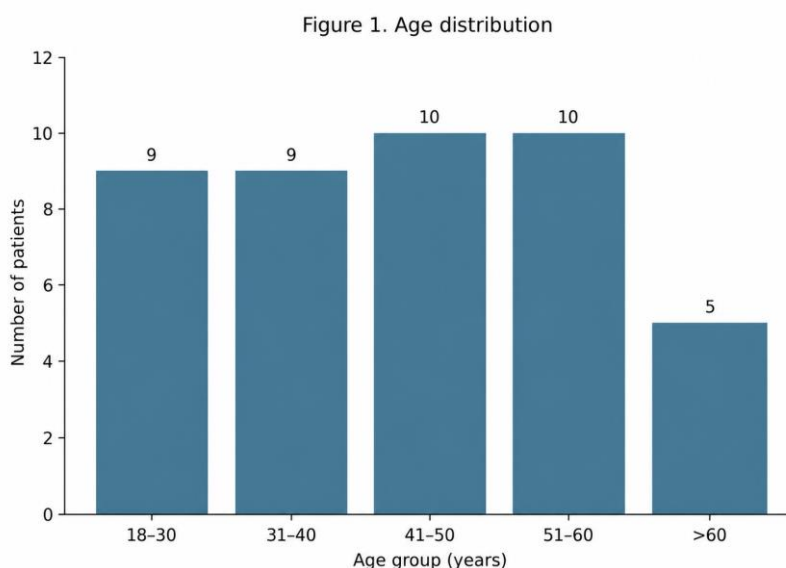


Figure 1. Age distribution of the study population (N = 43).

Colonoscopic findings

Colonoscopy was macroscopically normal in 38 patients (88.4%). Five patients (11.6%; 95% CI 3.9–25.1%) had an abnormality: an oedematous and ulcerated ileocaecal valve (1), mucosal oedema and hyperaemia (2), right colonic angioectasia (1) and a sigmoid diverticulum (1) (Table 3, Figure 2). Of these, the ulcerated ileocaecal valve and the mucosal oedema and hyperaemia, three patients in all (7.0%; 95% CI 1.5–19.1%), were inflammatory in character.

Table 3. Colonoscopic findings (N = 43)

Colonoscopic finding	n	%
Normal colonoscopy	38	88.4
Oedematous and ulcerated ileocaecal valve	1	2.3
Mucosal oedema and hyperaemia	2	4.7
Right colonic angioectasia	1	2.3
Sigmoid diverticulum	1	2.3

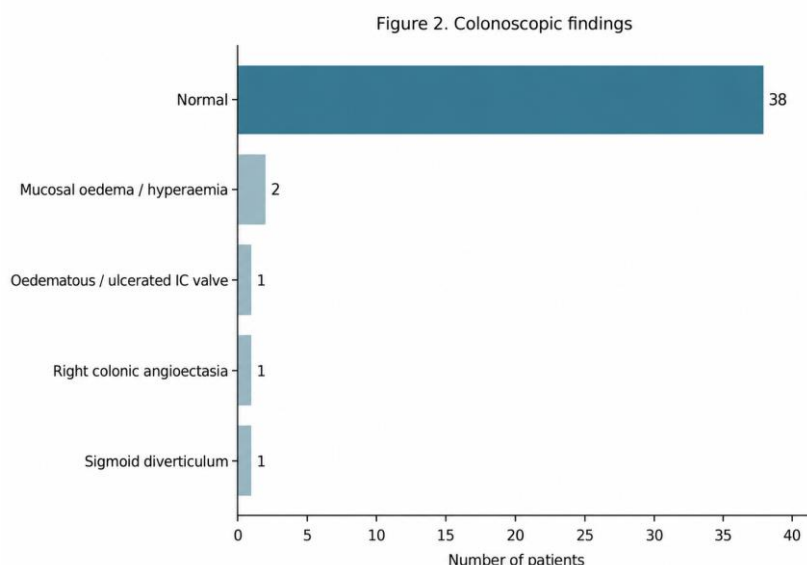


Figure 2. Colonoscopic findings (N = 43).

Histopathological findings

Histology was normal in 18 patients (41.9%) and abnormal in 25 (58.1%; 95% CI 42.1–73.0%). Nonspecific colitis was the most frequent abnormality (14 patients, 32.6%), followed by lymphocytic colitis (6, 14.0%) and eosinophilic colitis (2, 4.7%). Ulcerative colitis, Crohn's disease and intestinal tuberculosis were each diagnosed in one patient (2.3%) (Table 4, Figure 3). A specific histological diagnosis was therefore made in 11 patients (25.6%; 95% CI 13.5–41.2%).

Table 4. Histopathological diagnosis (N = 43)

Histopathological diagnosis	n	%
Normal histology	18	41.9
Nonspecific colitis	14	32.6
Lymphocytic colitis	6	14.0
Eosinophilic colitis	2	4.7
Ulcerative colitis	1	2.3
Crohn's disease	1	2.3
Intestinal tuberculosis	1	2.3

Percentages sum to 100.1% because of rounding.

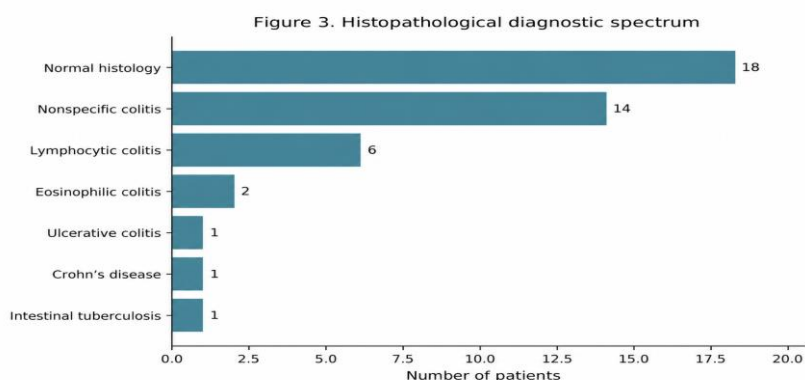


Figure 3. Histopathological diagnostic spectrum (N = 43).

Diagnostic yield

Because only five colonoscopies were abnormal, at least 20 of the 38 macroscopically normal colonoscopies ($\geq 52.6\%$) must have had a histological abnormality, and at least six ($\geq 15.8\%$) must have yielded a specific histological diagnosis. These minimum estimates are summarised in Table 5.

Table 5. Diagnostic yield of colonoscopy and histopathology (N = 43)

Measure	n	% (95% CI)
Macroscopic abnormality at colonoscopy	5	11.6 (3.9–25.1)
Inflammatory colonoscopic finding	3	7.0 (1.5–19.1)
Any histological abnormality	25	58.1 (42.1–73.0)
Specific histological diagnosis	11	25.6 (13.5–41.2)
Lymphocytic colitis	6	14.0 (5.3–27.9)

CI, exact (Clopper–Pearson) confidence interval.

Lymphocytic colitis

Six patients (14.0%) had lymphocytic colitis. Four (66.7%) were women and the mean age was 51.5 ± 11.4 years. The mean duration of diarrhoea was 7.5 ± 4.1 months. All six had watery diarrhoea; five (83.3%) had nocturnal diarrhoea and five (83.3%) abdominal pain, two (33.3%) had weight loss, and none had fever. Nocturnal diarrhoea was more frequent in lymphocytic colitis than in the remaining patients (5 of 6, 83.3%, vs 12 of 37, 32.4%; Fisher's exact $P = 0.028$), although this unadjusted post hoc comparison rests on very few patients. Associated conditions were hypothyroidism in two patients (33.3%), rheumatoid arthritis in one (16.7%) and smoking in two (33.3%); none had type 1 diabetes mellitus or coeliac disease (Table 6).

Table 6. Characteristics of patients with lymphocytic colitis (N = 6)

Characteristic	Value
Age, years, mean $\pm$ SD	51.5 ± 11.4
Female, n (%)	4 (66.7)
Male, n (%)	2 (33.3)
Duration of diarrhoea (months), mean $\pm$ SD	7.5 ± 4.1
Watery diarrhoea, n (%)	6 (100)
Nocturnal diarrhoea, n (%)	5 (83.3)
Abdominal pain, n (%)	5 (83.3)
Weight loss, n (%)	2 (33.3)
Fever, n (%)	0 (0)
Smoking (present or past), n (%)	2 (33.3)
Hypothyroidism, n (%)	2 (33.3)
Rheumatoid arthritis, n (%)	1 (16.7)
Type 1 diabetes mellitus, n (%)	0 (0)
Coeliac disease, n (%)	0 (0)

Associated factors may overlap within a patient.

Histology in relation to IBS-D

Twenty patients (46.5%) fulfilled Rome III criteria for IBS-D and 23 (53.5%) did not (Figure 4). Among the 20 with IBS-D, histology was normal in 6 (30.0%), showed nonspecific colitis in 9 (45.0%), lymphocytic colitis in 4 (20.0%; 95% CI 5.7–43.7%) and eosinophilic colitis in 1 (5.0%) (Table 7, Figure 5). A histological abnormality was therefore present in 14 of 20 patients with IBS-D (70.0%), compared with 11 of 23 without (47.8%; $P = 0.22$). Lymphocytic colitis was found in 4 of 20 (20.0%) and 2 of 23 (8.7%; 95% CI 1.1–28.0%) respectively ($P = 0.39$). Ulcerative colitis, Crohn's disease and intestinal tuberculosis were all diagnosed in patients who did not fulfil IBS-D criteria (3 of 23, 13.0%) and in none of those who did. Patients with lymphocytic colitis who fulfilled IBS-D criteria ($n = 4$) were more often older than 50 years than the 15 patients with IBS-D and normal histology or nonspecific colitis (3 of 4, 75.0%, vs 5 of 15, 33.3%; $P = 0.26$). The female-to-male ratio was approximately 2:1 and 2.3:1 respectively, and the mean age of the latter group was 48 ± 15.4 years.

Table 7. Histopathological diagnosis by IBS-D status (Rome III)

Histopathological diagnosis	IBS-D (n = 20), n (%)	Not IBS-D (n = 23), n (%)
Normal histology	6 (30.0)	12 (52.2)
Nonspecific colitis	9 (45.0)	5 (21.7)
Lymphocytic colitis	4 (20.0)	2 (8.7)
Eosinophilic colitis	1 (5.0)	1 (4.3)
Ulcerative colitis	0 (0)	1 (4.3)
Crohn's disease	0 (0)	1 (4.3)
Intestinal tuberculosis	0 (0)	1 (4.3)

IBS-D, diarrhoea-predominant irritable bowel syndrome (Rome III criteria).

Figure 4. Initial clinical IBS-D classification

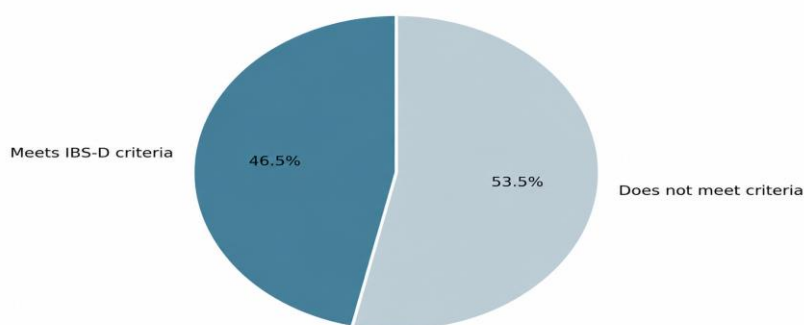


Figure 4. Classification of patients by Rome III criteria for IBS-D (N = 43).

Figure 5. Histopathological findings by initial IBS-D classification

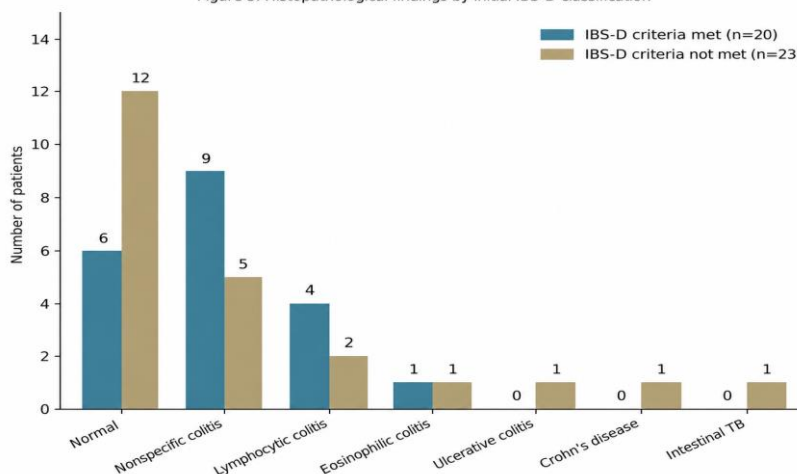


Figure 5. Histopathological findings by IBS-D classification (IBS-D, n = 20; not IBS-D, n = 23).

DISCUSSION

In this study of 43 patients with chronic watery, non-bloody diarrhoea, colonoscopy was macroscopically normal in 88.4%, yet mucosal biopsy showed a histological abnormality in 58.1% and established a specific diagnosis in 25.6%. Because only five colonoscopies were abnormal, at least half of the macroscopically normal examinations must have carried a histological abnormality. The central message is that, in this population, the endoscopic appearance alone would have missed most of the diagnostic information, which is consistent with the long-standing observation that biopsy adds substantially to colonoscopy in chronic diarrhoea [3].

Microscopic colitis. Lymphocytic colitis was the most frequent specific diagnosis, found in 14.0% of patients (95% CI 5.3–27.9%). This is of the same order as, or somewhat above, the proportion usually quoted for patients investigated for chronic watery diarrhoea [4,6], although our confidence interval is wide and the estimate should not be over-interpreted. No collagenous colitis was identified, in contrast to an Indian tertiary-centre series of microscopic colitis in which it accounted for 7 of 29 cases and men predominated (75.8%) [12]. The clinical profile of our lymphocytic colitis patients matched the established phenotype: female predominance, a mean age above 50 years, and a high frequency of nocturnal diarrhoea [4,5,11]. Nocturnal diarrhoea in particular distinguished these patients from the rest of the cohort (83.3% vs 32.4%), which supports its use as a clinical prompt for biopsy, although the comparison is post hoc and based on only six patients. Hypothyroidism (two patients) and rheumatoid arthritis (one patient) were also present, in keeping with the recognised association of microscopic colitis with autoimmune disease [4,5]; smoking, another recognised association supported by meta-analysis and cohort data [14,16,17], was reported by two of six patients.

Overlap with IBS-D. Nearly half the cohort (46.5%) fulfilled Rome III criteria for IBS-D, and histological abnormalities were at least as common in this group as in those who did not (70.0% vs 47.8%). Lymphocytic colitis was found in one in five patients with IBS-D (4 of 20). The differences were not statistically significant with these numbers, and the study was not powered to detect them. They nonetheless illustrate the practical point that satisfying symptom-based criteria does not exclude a histologically defined colitis, in line with pooled data linking IBS-type symptoms with microscopic colitis [8], with population-based data showing that about half of patients with microscopic colitis meet symptom-based IBS criteria [13], and with a recent series in which 10 of 89 patients with IBS-D (11.2%) had microscopic colitis [15]; the overlap is reviewed in [18]. Patients with IBS-D who had lymphocytic colitis tended to be older than those with normal histology or nonspecific colitis (75.0% vs 33.3% older than 50 years), suggesting that new-onset IBS-D symptoms in later life merit a low threshold for biopsy.

Nonspecific colitis. Nonspecific colitis was the largest histological category after normal histology (32.6%), and was especially frequent in the IBS-D group (45.0%). Its significance is uncertain: it may represent resolving infection, drug effect, a subtle or early inflammatory process or low-grade inflammation of unclear origin. We did not have follow-up data to establish its natural history, and this category deserves prospective study, including whether it predicts later inflammatory bowel disease or microscopic colitis.

Other diagnoses. Eosinophilic colitis, ulcerative colitis, Crohn's disease and intestinal tuberculosis together accounted for five patients (11.6%). The latter three were all found in patients who did not meet IBS-D criteria. In regions where tuberculosis and inflammatory bowel disease can coexist and overlap clinically and endoscopically, the single case of intestinal tuberculosis is a reminder that ileocaecal abnormalities need histological, and where appropriate microbiological, assessment before treatment is chosen.

Practical implications. Our findings support taking biopsies from a macroscopically normal colon in chronic non-bloody diarrhoea, as current guidelines recommend [2,5], and caution against assigning an IBS-D diagnosis before histology is available in patients with nocturnal diarrhoea, older age or an associated autoimmune disease.

Limitations

The sample was small (N = 43) and the confidence intervals for most proportions are wide. Only six patients had lymphocytic colitis, so associations with age, sex, nocturnal diarrhoea and autoimmune disease are descriptive and could not be tested in a multivariable model; the P values reported are unadjusted and exploratory. The study was single-centre and drawn from a tertiary referral population, which may limit generalisability. Endoscopic and histological findings were not cross-tabulated, so we can state only minimum figures for the yield of biopsy in macroscopically normal colons. IBS-D was classified by the Rome III rather than the current Rome IV criteria. No follow-up data were available; therefore, treatment outcomes and the natural history of nonspecific colitis could not be assessed.

CONCLUSION

In patients with chronic non-bloody diarrhoea, colonoscopy was macroscopically normal in nearly nine out of ten, whereas histology identified an abnormality in 58.1% and a specific diagnosis in 25.6%, with lymphocytic colitis the commonest.

Histological abnormalities, including lymphocytic colitis, were frequent among patients who met Rome III criteria for IBS-D. Mucosal biopsies should therefore be obtained from a macroscopically normal colon in chronic non-bloody diarrhoea, and a symptom-based diagnosis of IBS-D should not replace histological evaluation. Larger, multicentre studies with follow-up are needed to confirm these findings and to clarify the clinical significance of nonspecific colitis.

DECLARATIONS

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Conflicts of interest: None.

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