

Editorial

Just Do Not Stop at Colonoscopy, Obtain Biopsies

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Chronic, nonbloody, large bowel type of diarrhea is defined as abnormal (>3–4 times per day) passage of stool of reduced consistency lasting for >4 weeks.^[1] Though there are regional variations to this definition, nearly about 3%–20% of children and 4%–5% of the adult population experience chronic, nonbloody diarrhea and seek medical advice.^[2] Evaluation of these patients needs careful clinical workup to narrow down the exact etiology from a long list of possible causes, such as functional bowel disease, lactose malabsorption, inflammatory bowel diseases (IBDs), microscopic colitis, Whipple's disease, amebiasis, bile acid diarrhea, drug-induced diarrhea, pseudomembranous colitis, postradiation diarrhea, endocrinopathy-associated diarrhea, neuroendocrine tumors, granulomatous colitis, amyloidosis, melanosis coli, and fecal incontinence or fecal urgency.^[3] The British Society of Gastroenterology has recommended a set of first-line investigations to rule out the common causes of chronic diarrhea such as celiac disease, IBD, diarrhea-predominant irritable bowel syndrome, and large bowel tumors, along with a set of second-line investigations in patients where first-line investigations fail to identify the causes of persistent diarrhea and malabsorption.^[1] Similar guidelines were also given by the American Gastroenterological Association Clinical Practice and Practice Economics Committee.^[4] In summary, patients with chronic diarrhea under 40 years without typical symptoms of functional bowel disorder and/or having severe symptoms should undergo a detailed evaluation.^[1,4]

In the present issue, Lee *et al.* published an article including 182 patients with chronic diarrhea, of whom 86 patients met the inclusion criteria.^[5] They obtained colonic biopsies from them even if the colonic mucosa appeared normal macroscopically. On histological evaluation, the colon showed abnormalities in 51 (59.3%) of them and the rest had normal mucosa (35 [40.7%]). The abnormalities reported by them included nonspecific

inflammation in 29 patients, lymphocytic colitis in 12 patients, eosinophilic colitis and tuberculosis in 3 patients each, and IBD in 4 patients. Furthermore, among 22 patients (25.5%) with diagnostic histology, 21 (95.4%) patients had diagnostic histological changes from the biopsies obtained from the right colon, whereas only 9 (40.9%) patients had diagnostic histological changes from the rectosigmoid region. Of 12 patients with lymphocytic colitis, left colon biopsies fulfilled the diagnostic criteria in only four patients, whereas right colon biopsies were diagnostic in all the 12 patients.^[5]

The present study addresses two issues: first, during the evaluation of patients with chronic, nonbloody diarrhea, multifocal mucosal biopsies should be obtained both from the colon and terminal ileum even if the mucosa appears macroscopically normal. Second, should a sigmoidoscopic examination or a full-length colonoscopy along with retrograde ileoscopy be performed in such patients?

Whether a 60-cm flexible sigmoidoscopy or a full-length colonoscopy will suffice in these patients to identify the etiology of nonbloody diarrhea is still a matter of debate. While the sigmoidoscopic examination is favorable in terms of cost, availability, rapidity, and easy patient preparation, there are, however, chances of missing the patchy pathological lesions and lesions limited to the proximal large bowel or the terminal ileum. Khanna *et al.* compared the utility of sigmoidoscopy with biopsy versus full-length colonoscopy with terminal ileal evaluation and biopsy in patients with chronic diarrhea. Histologically confirmed diagnosis could be achieved in 31.5% of cases based on colonoscopic biopsies, 9.5% with ileoscopic biopsies, and in only 12.4% with recto-sigmoidoscopic biopsies alone.^[6] The changes of microscopic colitis, though are often diffuse, can also be detected only in the proximal colon. Routine ileoscopy

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in addition to these does contribute an additional diagnostic yield in 18% of non-HIV patients with chronic diarrhea.^[7] More importantly, in a proportion of patients with chronic diarrhea, the terminal ileum can show pathological lesions, even when the whole colon appears normal.^[7,8]

While endoscopic visualization can identify altered vascular patterns, mucosal ulcerations, pseudomembranous colitis, polypoidal tumors, and melanosis coli, many diseases of the colon such as microscopic colitis, amyloidosis, and granulomatous colitis may have a macroscopically normal mucosa.^[9] Hence, a diagnosis can be missed if one relies only on the endoscopic visualization of the mucosa without adequate tissue sampling. Geboes *et al.* reported that diagnostic yield increased up to 50% when mucosal biopsies were taken from suspected pathological changes under endoscopic visualization.^[9] Overall, combined full-length colonoscopy and ileoscopy with biopsy can increase the diagnostic yield up to 15%–20% in patients with chronic, nonbloody diarrhea.^[11] Consideration of full-length colonoscopy if the flexible sigmoidoscopy findings remain inconclusive is another standard method of approach in symptomatic patients with persistent diarrhea. Overall, it seems that combined full-length colonoscopy and retrograde terminal ileal evaluation is more appropriate than isolated short-length sigmoidoscopic evaluation in patients presenting with chronic, nonbloody diarrhea.

Mucosal biopsies should always be taken from any suspicious area under endoscopic visualization, and random four-quadrant biopsies should be taken from macroscopically normal ileum, cecum, ascending colon, transverse colon, descending colon, and rectosigmoid colon to increase diagnostic yield, as was demonstrated in the present article as well as by Lee *et al.*^[5] Biopsy fragments from all these areas should be sent to the pathologist in separately labeled vials for better identification of the specific site of pathology.

As described in this issue by Karri *et al.*^[10] and others such as Lee *et al.* and Kagueyama *et al.*, a significant number of patients in their series were labeled as having nonspecific colitis.^[5,11] Nonspecific colitis is not a diagnostic category, but it merely represents the nonspecific nature of the inflammation present in the colonic biopsies. It is, therefore, essential for the pathology colleagues to avoid the use of such terminologies while reporting the histological features. In such cases, colonic mucosa with increased chronic inflammatory cell infiltrate in lamina propria; maintained crypt architecture, without any feature of neutrophilic activity; basal plasmacytosis; or

granulomas are expected, and one may describe and conclude with a comment on the nonspecific nature of these inflammatory changes. Furthermore, an unqualified diagnosis of microscopic colitis is not recommended, and a distinction between collagenous and lymphocytic colitis should be made. Often, pathology reports use the term “consistent with” or “in keeping with” or “compatible with,” which also may be overrelied upon and misinterpreted. In such cases, the degree of certainty should be conveyed.

We would like to highlight a couple of additional points. First, the clinician and the endoscopist should provide appropriate clinical and imaging details including possible differential diagnosis, which help a pathologist in the interpretation of pathological findings in light of clinical possibility. While in many cases, the pathological diagnosis is self-evident and clinical details may not have any great bearing. More commonly, the pathological characteristics are interpreted in light of clinical details. Second, a multidisciplinary approach including discussion between clinicians, pathologists, and radiologists or other appropriate specialists often helps in solving the diagnostic mysteries. Hence, a combined effort of the gastroenterologists and pathologists can improve the diagnostic yield in endoscopic mucosal biopsy.

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