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Review Article

Is Biopsy Necessary if Colonoscopy is Normal in Patients With Chronic Unexplained Diarrhea?

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Endoscopy and biopsy are important diagnostic tools in the evaluation of patients with chronic diarrhea and normal colonic mucosa. When colonoscopy is performed in patients with diarrhea and normal endoscopic appearance, representative sampling is important to rule out not just irritable colon but other conditions such as inflammatory bowel disease, collagenous colitis, lymphocytic colitis, eosinophilic colitis and amyloidosis. Clinically important histological lesions can be identified in a significant proportion of patients in spite of normal or nonspecific colonoscopic findings, which justifies routine mucosal biopsy in the evaluation of patients with chronic diarrhea. It is recommended that when colonoscopy is performed for the evaluation of patients with diarrhea of unknown cause and mucosa appears normal, five biopsy sites be sampled, including the cecum, transverse colon, descending colon, sigmoid colon and rectum.

INTRODUCTION

Diarrheal disease can be divided into acute and chronic forms. Acute diarrhea is commonly due to infectious pathogens, is often self-limiting, and most patients do not require specific therapy (1). In patients with chronic diarrheal disease, the individual case history is of paramount importance for differentiation between functional and organic illness. At least half of patients in the general practice suffer from functional rather than organic disease. Endoscopy of the gastrointestinal tract is the first-line procedure in patients with chronic diarrhea (2). In a large proportion of patients with chronic diarrhea, colonoscopy may show one or more forms of abnormalities ranging from congestion, hemorrhage, edema, stenosis, erosions, pseudomembranes, and ulceration of the colonic mucosa. A number of studies have suggested that colorectal biopsies should be routinely obtained at endoscopy in patients with normal appearing mucosa who present with chronic diarrhea, because significant pathology may be identi fied on histopathological examination (3-6). Possible abnormalities include inflammatory bowel disease (IBD), collagenous colitis, lymphocytic (microscopic) colitis, infectious colitis, eosinophilic colitis, amyloidosis, and AIDS-associated diarrhea.

In Japan, endoscopists tend to diagnose irritable bowel syndrome (IBS) when patients with chronic diarrhea exhibit normal endoscopic features although no colonic biopsy is taken for histopathological examination. An important issue in the clinical management of such patients is, therefore, whether the endoscopist should take a biopsy when confronted with an apparently normal colorectal mucosa.

The lamina propria of colonic mucosa normally contains lymphocytes, plasma cells, eosinophils, and a few neutrophils. Increased number of such cells is considered to reflect the presence of colonic inflammation. However, the number of cells present in the normal mucosa has not been clearly established, and pathologists tend to overdiagnose the physiologic inflammatory infiltrate as evidence of colitis and underdiagnose specific etiologic types of colitis (7).

In this review, I will try to provide the endoscopist with insights into why and when to perform a biopsy of normally appearing colorectal mucosa in patients with chronic diarrhea.

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Crohn's disease

Crohn's disease is characterized by the presence of longitudinal ulcers and aphthous ulcers in the small intestine and colon, with non-caseous granuloma formation (Fig. 1A). Furthermore, biopsies from macroscopically normal mucosa in patients with Crohn's disease can show diagnostic abnormalities (8, 9). The characteristic morphology of mildly active Crohn's dis ease in colonic biopsies includes lymphoplasmacytic and neutrophilic inflammation and infrequent granulomas or giant cells. Inflammation is often patchy and can be associated with aphthoid ulcer, and therefore, multiple biopsies and serial sections are recommended for the diagnosis of Crohn's disease (10). There is usually glandular architectural distortion (11).

Focal cryptitis is often detected in the colonic mucosa of patients with Crohn's disease (Fig. 1B), which may represent an early stage in the evolution of Crohn's disease (12, 13). However, this feature is non-specific and may also be seen in ischemia, infections, partially treated ulcerative colitis (14, 15). This emphasizes the importance of obtaining a biopsy from apparently uninvolved mucosa, proximal or distal to the lesions.

Ulcerative colitis

Ulcerative colitis affects contiguous areas of the colon and is most severe in the rectum, however, endoscopic and histological patchiness of inflammation and rectal sparing are common during the course of the disease in treated ulcerative colitis. Therefore, rectal sparing or patchiness should not necessarily indicate a change in the diagnosis to Crohn's disease (16-19). A number of investigators have stressed that the relapse index is significantly higher in patients with rectal sparing (17), however, complete histologic sparing of the rectum is not rare (16). In general, endoscopic appearances of ulcerative colitis during the resolving or quiescent stages do not correlates well with histological findings as they do in the acute phase. The mucosa in ulcerative colitis usually regenerates so well that it is often virtually indistinguishable from the normal mucosa on histological examination (20,21), however, architectural distortion, which indicates previous damage to the involved crypt, is often seen (Fig. 2), making it possible to diagnose quiescent ulcerative colitis (11).

Patients with ulcerative colitis treated by 5-aminosalicylic acid (5-ASA) rarely have diarrhea despite the effect of 5-ASA on arachidonic acid metabolism. The incidence of diarrhea is 13-20% in olsalazine and 5% in mesalamine-treated patients (22, 23). Histologically, infiltration of the mucosa with eosinophils coalescing in areas to form eosinophilic crypt abscesses often correlates with clinical symptoms. The clinical problem is difficult because the dose of 5-ASA necessary to control ever-increasing disease. When 5-ASA sensitivity is suspected, topical challenge may show profound microscopic change during a short period of time.

Collagenous colitis

Collagenous colitis is characterized by chronic watery diarrhea associated with microscopic mucosal inflammation and deposition of collagen below the surface epithelium of the colonic mucosa (Fig. 3-B). There are generally no or minimal endoscopic abnormalities (Fig. 3-A), and colorectal biopsy is required to establish the diagnosis (24). In Japan, this is a very rare disease, and we have only encountered one case in our institution. This disease predominantly affects middle-aged elderly women. Typically, the patient presents with a history of chronic, non-bloody, watery diarrhea, of up to 20 bowel movements per day, for months or years. The etiology of collagenous colitis is still unclear, although a variety of associated diseases have been reported including gastrointestinal diseases such as collagenous sprue (25, 26) as well as systemic diseases such as rheumatic syndromes (27, 28) and thyroid diseases (28, 29). Riddell and colleagues (30) indicated that non-steroidal anti-inflammatory drugs(NSAIDs) use is common among patients with collagenous colitis (30). They also warned that in some cases, diarrhea followed the use of NSAIDs in all patients and that it improved after withdrawal of NSAIDs. Cimetidine rarely causes watery diarrhea (31). However, its role in the pathogenesis of collagenous colitis remains unsettled.

The thickness of subepithelial collagen deposits has been reported by some to be predominant in the right colon, especially the transverse colon (32-34), although others have not observed this regional variation (35, 36). The normal subepithelial basement membrane has a minimum thickness of 4 μm, but in collagenous colitis this sometimes exceeds 30 μm (37). Thickening of the collagen plate above 10 μm has been recently proposed as the threshold criterion for histological diagnosis of collagenous colitis (32, 35). This variability in the reported thickness between different groups of investigators might be due to several methodological

differences, including fixation, orientation, and methods of analysis (38, 39). Goff et al (40) found no significant difference in collagen thickness, epithelial damage, lamina propria cellularity, or lamina propria eosinophilia between patients reporting resolution of clinical symptom and those with ongoing symptoms. Conversely, Lee et al (41) studied patients with lymphocytic and collagenous colitis and found that stool weight correlated with lamina propria cellularity but not with collagen thickness.

It is important to stress that the perceived thickness of the collagen band alone is not sufficient for the diagnosis of collagenous colitis. There is almost always an associated increase in inflammatory cells such as lymphocytes, plasma cells, mast cells and macrophages. Mast cells and macrophages are widely distributed throughout the gastrointestinal mucosa and form the major source of inflammatory mediators. Schwab et al (42) reported mast cell activation in collagenous colitis, and we found that the numbers of mast cells and macrophages were different in patients with collagenous colitis than in those with Crohn's disease and ulcerative colitis (43). Our results also suggested that collagenous colitis is more of Th2 type reaction than Th1.

Prognosis varies widely in this disease, and prednisolone is most effective with a response rate of 80% (40, 44), while that of 5-ASA is 40-60% (45, 46). However, treatment-free remissions are common in collagenous colitis (47).

Lymphocytic colitis (Microscopic colitis)

Lymphocytic colitis (LC) is classically described as a triad of chronic non-bloody, watery diarrhea, normal or near-normal endoscopic findings, and colonic epithelial lymphocytosis without thickening of the subepithelial collagen table. Read et al (48) reported a mild increase in inflammatory cells in biopsy specimens of a number of patients with chronic diarrhea who had in significant colonoscopic finding and coined the term "microscopic colitis" to describe this form of diarrheal disease. Subsequently, Lazenby et al (49) showed that increased number of colonic intraepithelial lymphocytes was the major distinguishing feature in many of the patients with microscopic colitis and therefore proposed the term lymphocytic colitis to identify that subgroup.

Normally, there are five or fewer lymphocytes per 100 epithelial cells, but this is markedly increased in lymphocytic colitis to 20-40/100 epithelial cells (Fig. 4). In this regard, Wang et al (51) proposed that the criterion for diagnosis was the presence of at least 15 surface lymphocytes per 100 epithelial cells. Intraepithelial lymphocytes in lymphocytic colitis are mostly CD8-positive (50), and they are overlying lymphoid follicle that have an antigen-presenting function, termed M cells.

Colonic epithelial lymphocytosis is not only seen in lymphocytic colitis (24, 51), but also in collagenous colitis (29, 52), as well as in some cases of celiac sprue (50, 53). Recently, this histologic finding has also been reported in epidemic outbreaks of apparently infectious diarrhea, Brainerd diarrhea (54-58). The term Brainerd diarrhea has been applied to outbreaks of chronic watery diarrhea of unknown etiology characterized by acute onset and prolonged duration. Patients are more likely to be travelers with a history of drinking unbottled water or ice or consumed raw sliced fruits and vegetables washed in unbottled water (56-58). Patients with Brainerd diarrhea often do not respond to antimicrobial therapy (57, 58). Colonoscopy in these patients show normal mucosa or patchy erythema, and colonic biopsy specimens frequently show epithelial lymphocytosis similar to that seen in collagenous and lymphocytic colitis. Although Brainerd diarrhea can be currently diagnosed only with epidemiologic data indicating an epidemic and a point source, the lack of surface degenerative changes and the relatively lower lymphocyte counts may serve to distinguish it from lymphocytic colitis (58).

Infectious colitis

This is always a possibility and is probably the most difficult in the differential diagnosis. It is uncertain if these cases can be diagnosed if the full picture of infection is not present on the biopsy, particularly when symptoms have been present for weeks or months where extension of chronic inflammatory cells, especially plasma cells, may be seen down to the muscularis mucosae. Further, it should be remembered that chronicity does not exclude infection; Clostridium difficile may cause symptoms for months if left untreated (59), while even patients with infections such as Shigellosis and Salmonellosis may occasionally have chronic symptoms (60, 61).

Eosinophilic enterocolitis

Eosinophilic colitis remains a relatively poorly described disease entity in which diarrhea and eosinophilic infiltra tion of the colon often with peripheral eosinophilia pre dominate. The most common pathologic cause of eosinophilic accumulation is probably ulcerative colitis,

with numerous eosinophils present in the lamina propria (62, 63). In developing countries, parasitic infection such as Strongyloides (64), Ancylostoma caninum (65), and dog hookworm (66) is often associated with eosinophilic accumulation in the colon. Occasional case reports have described eosinophilic infiltration as a side-effect to several drugs including carbamazepine (67), rifanpicin (68), naproxen (69), and azathioprine (70). Serosal involvement is frequently accompanied by eosinophilic ascites. Colonic eosinophilia may also be part of the generalized eosinophilic vasculitis associated with Churg-Straus syndrome (71). In some biopsies from patients with these diseases, eosinophils may be prominent particularly beneath the luminal epithelium and sometimes within the epithelium (Fig. 5). Eosinophilic colitis in these conditions are characterized histologically by the presence of $>$ 20 eosinophils per high-power field (72, 73).

AIDS-associated diarrhea

Chronic diarrhea with malabsorption and weight loss is a common problem in AIDS patients. The causative organisms frequently identified in such cases are cytomegalovirus, adenovirus, cryptosporidium, microsporidia, mycobacterium avium complex (74, 75). Furthermore, bacterial pathogens are more common in AIDS patients than in the general population (76). Colonoscopy is commonly performed in patients with chronic human immunodeficiency virus (HIV)-related diarrhea after negative stool studies, and the test often shows normal or mildly inflamed mucosa. A pathogen is frequently identified in colonic biopsy specimens from patients with HIV-related chronic diarrhea, and therefore, the test is thought to be the most cost-effective diagnostic procedure (77). Microscopic examination shows foci of mucosal necrosis containing chronic inflammatory cells, degenerating and necrotic epithelial cells with amphophilic nuclear inclusions. Transmission electron microscopic reveals hexagonal viral particles characteristic of the causative virus within the nuclear inclusions (78).

Another entity known as idiopathic AIDS enteropathy is diarrhea in AIDS patients in whom secondary infectious agents cannot be identified. There is evidence to suggest that these changes occur in HIV carriers who do not exhibit clinical manifestations of AIDS (79).

Amyloidosis

Amyloidosis usually causes various gastrointestinal symptoms included diarrhea, anorexia, macroglossia, and intestinal pseudo-obstruction. Reactive systemic or secondary amyloidosis occurs in 1-30% of adults with Crohn's disease (80, 81). Colonoscopy commonly shows mucosal friability and erosions, but rarely shows normal appearance of the colonic mucosa. Rectal biopsy has the highest diagnostic yield, followed by duodenal, gastric, and colonic biopsies. Amyloid deposit is demonstrated principally in blood vessels and accompanies microscopic inflammation (82).

Irritable bowel syndrome (IBS)

IBS is a chronic disorder of the gastrointestinal tract. The etiology of irritable bowel syndrome is still unclear and the relationship between food and IBS is controversial. Psychiatric disorders have an adverse influence on the outcome of IBS, which is thought to be due to the close relationship between psychological symptoms and severity of abdominal pain, bloating, and diarrhea (83). Familiarity with both the distribution and intensity of normal inflammation is therefore essential, including the facts that (a) normal distribution of chronic inflammatory cells, particularly plasma cells, is limited to the upper two thirds of the mucosa, although macrophages, occasional lymphocytes, mast cells and eosinophils may invade the muscularis mucosae, (b) the severity of chronic inflammation is such that other than normal lymphoid aggregates, inflammatory cells are not tightly packed against each other (11). Few studies reported that rectal biopsy and lactose hydrogen breath testing are helpful in establishing the diagnosis of IBS (84), but their usefulness could not be confirmed by others (85, 86). There are also a few reports that have described infiltration of mast cells in IBS (87, 88), although this remains controversial (89).

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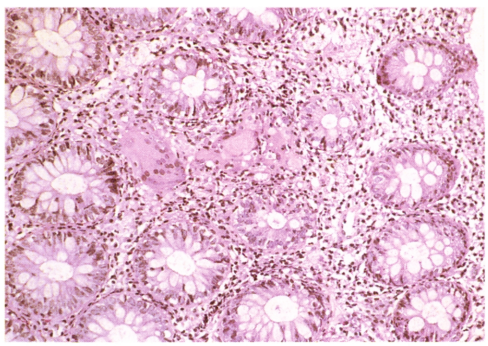

Fig. 1. (A)

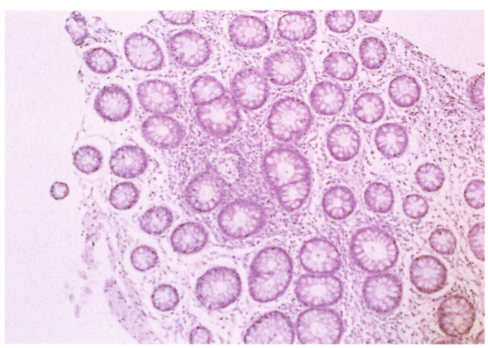

Fig. 1. (B)

Fig. 1. Crohn's disease. (A) Noncaseous granuloma with giant cells. Magnification, ×200, (B) Localized acute inflammatory process with focal cryptitis in the central area. Magnification, ×100

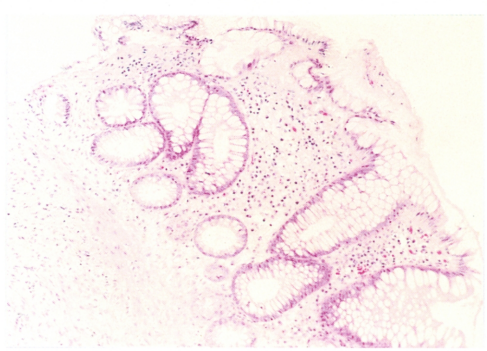

Fig. 2. Quiescent ulcerative colitis; Architectural distortion without neutrophils or basal plasmacytosis. Magnification,×100

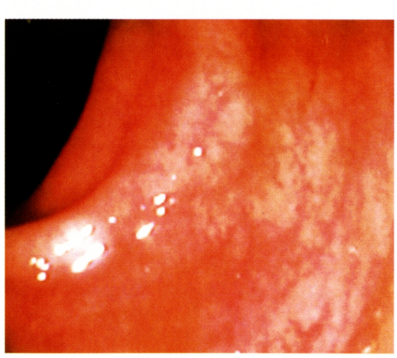

Fig. 3. (A)

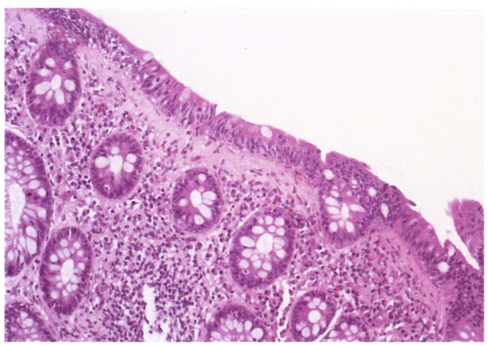

Fig. 3. (B)

Fig. 3. Collagenous colitis. (A) Colonoscopy in sigmoid colon showing almost normal colonic mucosa. (B) Thickening of subepithelial collagen band with numerous chronic inflammatory cells. Magnification,×100

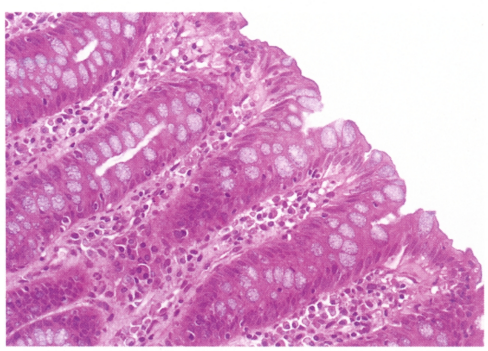

Fig. 4. Lymphocytic colitis; Note the intraepithelial lymphocytes with increased chronic inflammatory cells in the lamina propria. Magnification, ×200

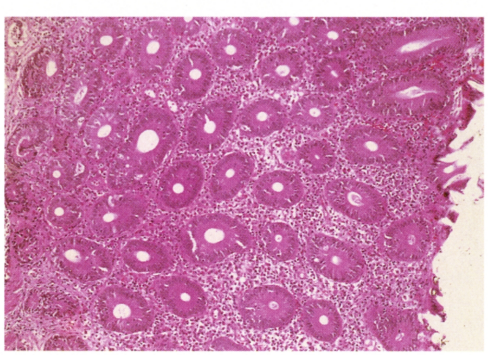

Fig. 5. Eosinophilic colitis. Note the presence of numerous eosinophils particularly beneath the luminal epithelium and occasionally in the epithelium. Magnification, ×100

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