Paucicellular and Asymptomatic Lymphocytic Colitis

Expanding the Clinicopathologic Spectrum of Lymphocytic Colitis

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Abstract

We examined clinicopathologic associations and biopsy changes that suggested classic lymphocytic colitis (C-LC) but were less well developed in intensity or distribution in 19 cases, which we termed paucicellular LC (P-LC). We also studied clinicopathologic associations and prevalence of LC in 100 asymptomatic, non–gluten-sensitive adults who underwent screening surveillance colonoscopy for previous adenoma. The control group was 38 randomly selected morphologically C-LC cases. The features of P-LC were foci of mildly increased lamina propria lymphoplasmacytic inflammation and increased surface intraepithelial lymphocytes separated by foci or tissue fragments of normal mucosa. Mean age and rates of female sex, endoscopically normal appearing colon, abdominal pain, watery stools, weight loss, connective tissue diseases, and consistent ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) were similar for P-LC and C-LC patients. Of 100 asymptomatic patients, 26 (26%) had LC and 43 (43%) used NSAIDs daily. Of these 43 patients, 14 (33%) had P-LC or C-LC. Daily NSAID ingestion was associated significantly with LC (P = .024). P-LC patients had clinicopathologic relationships similar to those of C-LC patients, suggesting they should be considered part of the morphologic spectrum of LC. LC in asymptomatic adults might be more common than previously thought and might not be associated with watery diarrhea syndrome.

Lymphocytic colitis (LC) is a well-characterized pattern of microscopic colitis with diffuse lamina propria lymphoplasmacytic inflammation and increased surface intraepithelial lymphocytes (IELs).1-6 Most of the cases included in LC studies had unequivocal morphologic features, including a dense surface IEL infiltrate to facilitate characterization and comparison with similar cases.3,4,7-13

During recent years we occasionally have encountered LC-like cases that fell outside the boundaries of the characteristic clinicopathologic manifestations. One group of cases had morphologic features that were less well developed, either in distribution or intensity, than the cases studied by other authors. The significance and clinicopathologic relationships associated with mild abnormalities below the diagnostic threshold of morphologically classic LC are not well studied. A second group of cases were asymptomatic, non–gluten-sensitive (celiac sprue) patients with LC. Unexpected LC in asymptomatic patients is not well studied. It might have associations different from those in symptomatic patients with watery diarrhea syndrome or altered bowel habits.

The present study had two goals: (1) to characterize the morphologic features of paucicellular LC and investigate whether affected patients had clinicopathologic associations similar to those of patients with classic LC and (2) to investigate the clinicopathologic associations of LC in asymptomatic, non–gluten-sensitive adults.

Materials and Methods

Definitions

Lamina propria lymphoplasmacytic inflammatory cells:
The density of lamina propria lymphoplasmacytic inflammatory
cells was normal if there was a decreased cell density gradient toward the muscularis mucosa. This gradient obscured the loose areolar connective tissue in the superficial half of the lamina propria but allowed it to be seen easily along the muscularis propria. Abnormal, mildly increased density of lymphoplasmacytic inflammation in the lamina propria resulted in loss of the normal gradient and produced an even, homogeneous cell density throughout the full thickness of the lamina propria.

Pattern of inflammation: The pattern of inflammation was classified as diffuse or patchy. Diffuse inflammation was defined as homogeneous, continuous inflammation. Patchy inflammation varied between 2 specified locations. Inflammation was classified as the same biopsy fragment (ie, patchy inflammation between areas within the same biopsy tissue fragment), between tissue fragments obtained from the same region of the bowel, or between tissue fragments from different regions of the colon.

Surface IEL score: The region with greatest density of surface IELs in each tissue fragment was evaluated to score the number of surface IELs per 100 enterocytes. The lowest, highest, and mean surface IEL scores at each named region of the colon were recorded, and these values were used to calculate the mean case surface IEL score.

Case Selection

Nineteen cases with mild lymphoplasmacytic inflammation of the lamina propria and increased surface IELs that suggested but fell short of a diagnosis of LC and with sufficient clinical information in the William Beaumont Hospital (Royal Oak, MI) computer system or in the primary physician patient records were identified from the daily assigned cases of one of us (N.S.G.) from January 1, 2000, to December 30, 2002. These cases were termed paucicellular LC. The distinctive features that separated paucicellular LC from LC were patchiness and a lower density of surface IELs such that the morphologic criteria of classic LC were not fulfilled. Cases were included in the study if the morphologic abnormalities were present on 3 or more tissue fragments from 2 or more separate regions of the colon, excluding the proximal ascending colon.

Two cases of classic LC per study case (n = 38) were selected randomly from the large group of cases accessioned during the same time as the study cases. Patients were matched for sex and age (± 1 year). All cases included as classic LC had mean case surface IEL scores of more than 20 IELs per 100 enterocytes.

Control group cases were 100 randomly selected patients for whom descending colon biopsy specimens were procured at the time of screening colonoscopy for previous colon polyps. These random biopsy specimens were obtained routinely by the patients’ gastroenterologists as part of the standard colonoscopy procedure. All control group patients were asymptomatic, and none had abdominal pain, weight loss, or altered bowel habits. The colonic mucosa was endoscopically normal, excluding concomitant polyps. Of the 100 asymptomatic patients in the polyp-surveillance colonoscopy control group, 38 (38%) were women. The mean and median patient ages were 57.8 and 61.4 years, respectively (range, 38-78 years; SD, 6.5 years).

None of the patients in the paucicellular LC, classic LC, or control groups had inflammatory bowel disease or gluten sensitivity.

The mean numbers of separate specimen containers submitted for patients with paucicellular or classic LC were 2.8 (range, 2-5 containers) and 2.4 (range, 1-4 containers), respectively. All ascending colon biopsy specimens were obtained from the distal ascending colon; none were from the cecum or the proximal ascending colon. The mean numbers of tissue fragments per specimen container in paucicellular and classic LC cases were 3.4 (range, 2-11 tissue fragments) and 4.6 (range, 2-10 tissue fragments), respectively. The mean total number of tissue fragments examined in paucicellular LC, classic LC, and control cases were 10.6, 11.1, and 1.7 (range, 1-3 tissue fragments), respectively. All biopsy specimens were submitted in 10% neutral buffered formalin. Each tissue block was sectioned at 3 levels separated by approximately 100 µm. Two section ribbons were made at each level and placed on separate slides. One slide from each level was stained with H&E, and the other slide was stored.

The Pearson $\chi^2$ statistic was used to test factors between groups. Yates corrected $\chi^2$ was used in factors with few samples. Paired and 2-sample $t$ tests were used to compare the factor means between groups. A $P$ value of .05 or less was considered a statistically significant association. Statistical analysis was performed using Systat, version 10.2 (SPSS, Chicago, IL).

Results

The majority of tissue fragments from the ascending and transverse colon had mildly increased lymphoplasmacytic inflammation in the lamina propria and mildly increased surface IELs that were distributed homogeneously across the breadth of some tissue fragments, while other fragments were normal. Other fragments were involved partially with interspersed regions of normal mucosa. A minority of biopsy fragments had increased lymphoplasmacytic inflammation of the lamina propria and normal-density surface IELs.
Biopsy specimens from the descending and sigmoid colon and rectum generally had patchy involvement within and between tissue fragments. Regions of mucosa with mildly increased surface IELs and lymphoplasmacytic inflammation of the lamina propria were interspersed between regions of normal mucosa. Some of the sigmoid colon and rectal biopsy specimens were minimally abnormal and were not diagnostic of paucicellular LC on their own accord.

Classic LC had the characteristic features of dense lymphoplasmacytic inflammation of the lamina propria and markedly increased surface IELs. The mean case surface IEL scores of paucicellular and classic LC groups were 11.1 and 29.3 IELs per 100 enterocytes, respectively. The mean surface IEL scores were lower in more distal biopsy specimens in classic and paucicellular LC case groups. The decrease was significant in classic LC cases (ascending colon = 37.3; sigmoid colon or rectum = 16.1; $P < .001$). The mean surface IEL score of rectal or sigmoid biopsy specimens in 26 of the 36 patients (72%) with biopsies from this region was less than 20 IELs per 100 enterocytes, of which 8 (22%) had scores of less than 12 IELs per 100 enterocytes.
Clinical Associations

The clinical features and associations of the paucicellular and classic LC groups were similar [Table 2]. Most patients were women. Ages in the paucicellular LC group ranged from 47 to 69 years and in the classic LC group from 35 to 70. Fewer than one third of patients in each of the groups were taking daily aspirin or regularly using nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs). The percentages of patients in the paucicellular and classic LC groups with endoscopically normal mucosa, abdominal pain, watery stools, altered bowel habits, weight loss, and autoimmune or connective tissue diseases were also similar.

Asymptomatic Polyp-Surveillance Colonoscopy Patients

Of 100 asymptomatic patients undergoing polyp surveillance, 43 (43%) were daily NSAID users at the time of colonoscopy [Table 3]. Of the 43 daily NSAID users, 29 (67%) had morphologically normal biopsy specimens, 11 (26%) had paucicellular LC, and 3 (7%) had classic LC.
Of the 100 asymptomatic patients, 74 (74%) had morphologically normal biopsy specimens, 22 (22%) had paucicellular LC, and 4 (4%) had classic LC. Of the 74 patients, 29 (39%) with morphologically normal biopsy specimens were daily NSAID users, as were 11 (50%) of 22 patients with paucicellular LC and 3 (75%) of 4 with classic LC. Daily NSAID ingestion was associated significantly with paucicellular LC or classic LC (\(P = .024\)).

**Discussion**

The morphologic features of LC are well described.\(^1\)-\(^6\),\(^9\),\(^12\),\(^15\),\(^16\) Most cases included in these studies had unequivocal histologic changes.\(^3\),\(^4\),\(^7\),\(^9\),\(^11\),\(^13\),\(^15\),\(^18\) Inclusion of only characteristic cases is a reasonable method when the study goal is to obtain a relatively homogeneous set of cases that can be characterized and compared with other patient groups; however, in our opinion, this approach does not accurately reflect the histologic spectrum of disease. Exclusion of cases with features other than the classic morphologic features might lead to misdiagnosis or underdiagnosis of clinically symptomatic patients.

We found the clinicopathologic associations in patients with paucicellular LC were similar to those of patients with classic LC. This suggests that paucicellular LC should be included in the morphologic spectrum of LC. A broader definition might be a more accurate reflection of the potential findings encountered in one individual against the backdrop of morphologic diversity within a large...
patient population. The spectrum of morphologic changes associated with watery diarrhea syndrome might be even broader than the changes investigated in the present study. Two recent studies found that patients with only increased lymphoplasmacytic inflammation of the lamina propria without increased surface IELs (termed microscopic colitis not otherwise specified) had clinicopathologic relationships similar to those of patients with classic LC.21,22 Although some authors recommend that the term colonic epithelial lymphocytosis be used for cases that do not fulfill all clinicopathologic criteria of classic LC,21,22 the similarities in clinicopathologic associations between the paucicellular and classic LC groups lead us to suggest that they be grouped together as one entity.

We found that biopsy tissue fragments from the sigmoid colon and rectum in paucicellular and classic LC often were morphologically similar. Mean surface IEL scores previously have been shown to be highest in the ascending colon and lowest in the sigmoid colon and rectum.9,21,23 One study reported a substantial decrease in 18% of patients with LC such that the surface IEL density in the rectosigmoid was below the diagnostic threshold of classic LC.21 Another study reported that rectal biopsy specimens in 8% of patients with LC were normal.24 We also observed lower mean surface IEL scores distally in patients with classic LC. Of the sigmoid colon and rectal biopsy specimens from these patients, 22% fell into the morphologic realm of paucicellular LC, while more proximal biopsy specimens had the morphologic features of classic LC. These findings highlight the importance of procuring tissue fragments from all regions of the colon in patients with watery diarrhea syndrome. A small number of biopsy specimens from only the distal colon might lead to a false impression of normalcy.

Of 100 random biopsy specimens from asymptomatic patients undergoing polyp surveillance, 26 revealed LC (paucicellular or classic). The significance of this finding is unclear. Earlier LC studies were almost exclusively of symptomatic patients with watery diarrhea, loose stools, or altered bowel habits. LC in an asymptomatic or nondiarrheal patient was considered unusual.25,26 Over time, the scope of investigation has expanded to include more diverse patient groups, including asymptomatic patients. One recent study found that 20 of 50 routinely biopsied patients with Hashimoto thyroiditis had LC.27 Only 5 of 20 patients with LC had diarrhea; the other 15 patients were asymptomatic. Although the patient groups are different, approximately 25% of patients in both studies had LC. Other authors have commented that LC could include patients without diarrhea,21,28 and LC occasionally has been the harbinger of active Crohn colitis.29 Together, these findings suggest that LC is more common than previously reported and can be found in a wide range of patients, including those who are asymptomatic and those without watery diarrhea syndrome.

We are cautious about interpreting our results to suggest that the prevalence of LC is increasing in asymptomatic adults. LC might be more common than previously thought simply because routine colon biopsies are being performed on a broader spectrum of patients. A similar phenomenon occurred in the incidence of gastric cardia mucosa intestinal metaplasia during the last decade. Gastric cardia mucosa intestinal metaplasia was uncommon when the squamocolumnar junctions of patients with endoscopically normal anatomy were not biopsied routinely.30 After biopsy of this region became standard practice, it was recognized that 15% to 25% of adult patients had gastric cardia mucosa intestinal metaplasia.31-33 Additional studies are clearly needed to determine the true prevalence of LC in asymptomatic adults.

Of 100 asymptomatic patients undergoing polyp surveillance, 43% were daily NSAID users. This percentage is similar to the 15% to 50% rate of NSAID use found in symptomatic patients, most of whom had watery diarrhea.8,12,18,20,21,23,26 The relatively high rate of NSAID use in the present study might reflect the widespread use of NSAIDs to reduce the rate of subsequent adenomas in this patient group. Some pathologists might be unaware of the widespread use of NSAIDs for lowering the rate of subsequent colonic adenomas.34-41

Of 26 patients with LC, 14 (54%) were daily NSAID users. This finding is opposite to the results of a study in which none of 6 asymptomatic NSAID-using patients had LC.42 We do not have an explanation for this disparity. It is interesting that the morphologic features of several NSAID-using asymptomatic patients in the present study with paucicellular LC were similar to some of the abnormalities observed in patients with symptomatic NSAID-induced colitis.43 Based on these observations, we believe that NSAIDs were the probable cause of LC in this patient group.

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References


