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Original Article

Association of lymphocytic colitis and lactase deficiency in pediatric population

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ABSTRACT

Characterized by colonic mucosa intraepithelial lymphocytosis, lymphocytic colitis is primarily an entity presented in the middle-aged to elderly patient population. Very few large series of lymphocytic colitis of childhood occurrence are available in the medical literature. Ten cases each of lymphocytic colitis and of colonic lymphocytosis of other diagnosis, all with duodenal disaccharidases analysis data, were collected from the files of our institution. The electronic medical records were reviewed and multiple variables were analyzed. The ten patients with lymphocytic colitis presented with diarrhea. Of these, three had abdominal pain. The age range was 2–18 years. Nearly all patients were Caucasian (90%) and 70% were female. Endoscopically, most had normal appearing colonic mucosa. Significant past medical history, family medical history and associated comorbidities included celiac disease, Down syndrome, juvenile arthritis and other autoimmune diseases. Interestingly, the most revealing observation was that the majority of cases (80%) were associated with lactase deficiency and, for the most part, gastrointestinal symptoms improved simply by treatment with Lactaid or avoidance of dairy products. This association is statistically significant. Our clinicopathological study indicates that the typical pediatric patient is a female Caucasian. A large of portion of the patients had associated lactase deficiency and improved on Lactaid supplement alone.

Introduction

The concept of lymphocytic colitis gradually came into the diagnostic mainframe after some major studies in the late 1980s [7,10]. This type of microscopic colitis (the term was first coined by Read in 1980 to characterize a group of patients with severe chronic diarrhea for which specific diagnoses were missing even after extensive investigation; the patients typically presented with chronic watery diarrhea and normal or near-normal endoscopy findings [22]. The other type of microscopic colitis is collagenous colitis, which shares many clinical features and a major histological feature with lymphocytic colitis–intraepithelial lymphocytosis, but also features a distinctly prominent subepithelial collagen band [11].

Hitherto, of microscopic colitis, the pediatric population study data had been very limited. One recent Canadian study of eleven cases reported five as lymphocytic colitis and the others as "nonspecific/eosinophilic colitis" [4]. To our knowledge, even individual case reports of lymphocytic colitis in the pediatric population are rare, though sporadic single case reports of collagenous colitis in children have accumulated to less than 20 cases, with the clinical characteristic of most of these cases tabulated in the supplemental table of Bechimol's paper in 2007 [15,20,24].

Our study is a large-series research attempt, to capture the distinctive clinicopathological features of lymphocytic colitis in the pediatric population, with the emphasis on clinicopathological correlation. We have some important findings to report, among which and the most important, is that for the first time, a possible link between lactase deficiency and lymphocytic colitis has been identified, and the implications derived from this observation cannot be understated. Of note, a recent report by Wiecek et al. seems to support this observation [25], which came to our attention since the article was first drafted.

Methods

With the approval of our Institutional Review Board, 17 presumptive microscopic colitis (lymphocytic colitis and collagenous

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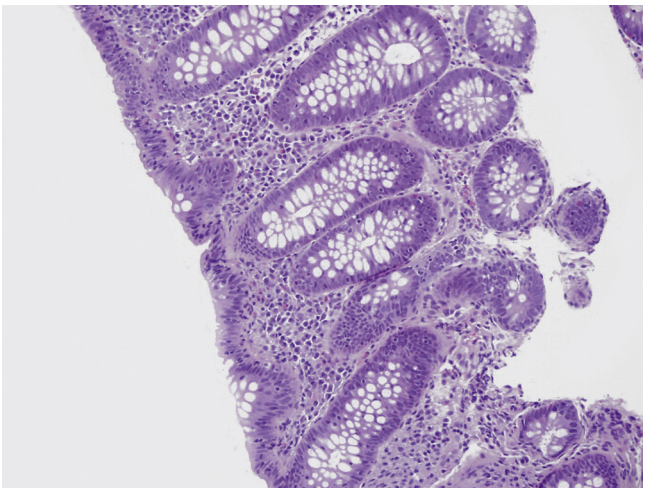

Fig. 1. Biopsy from a case histologically fits the criteria of lymphocytic colitis. Note the increased numbers of intraepithelial lymphocytes within the surface (luminal) epithelium and to a lesser extent within crypt epithelium. Occasional eosinophils are seen between luminal epithelial cells and in lamina propria. The luminal epithelium shows mild reactive changes/damages, but the crypt epithelium appears relatively normal. There are no granulomas or neutrophil infiltration anywhere in the biopsy to suggest other infectious or inflammatory bowel disease. But the finding per se is not specific. Many other causes of colonic intraepithelial lymphocytosis have the identical or similar histological appearance at biopsy level. The search for these other causes (celiac disease, inflammatory bowel disease, infectious, medication, immunodeficiency, etc.) is critical before rendering the diagnosis of lymphocytic colitis.

colitis) cases were first retrieved from the electronic pathology files of our pathology department from 2001 to 2012. Relevant clinical files from electronic medical records were also collected. All these cases featuring colonic intraepithelial lymphocytosis were reviewed with the strictest conventional diagnostic standards for lymphocytic colitis: absence of subepithelial collagen deposition; increased intraepithelial lymphocytes, greater than 20 per 100 colonic enterocytes; and accompanied by lamina propria, mixed inflammatory infiltrates, and variable degrees of surface epithelial injury [13]; when multiple sites were biopsied, all sites must fulfill the above criteria to be included. Borderline cases, such as so called paucicellular lymphocytic colitis, were also excluded. A representative lymphocytic colitis case is shown in Fig. 1.

All the major differential diagnoses were again considered, including collagenous colitis, refractory celiac disease (lymphocytic enterocolitis), acute colitis (especially resolving phase of infectious colitis), autoimmune enteropathy, inflammatory bowel disease, and medication-associated colonic lymphocytosis. These cases were excluded. An age and gender matched control group was carefully constructed by searching the same database for colonic intraepithelial lymphocytosis, cases in which when correlated with accurate clinical and laboratory data are thought to be incompatible with the diagnosis of lymphocytic colitis. Ten consecutive cases were collected. The gender composition of this control group was also 7:3 (female:male), same as our subject group. The mean age of the control group was 10.8 years, very close to our subject group (10.2 years). The most likely explanation of colonic intraepithelial lymphocytosis in our control group thus constructed included post infectious, medication, inflammatory bowel disease, collagenous colitis, celiac disease, etc.

The determination of gastrointestinal tract tissue lactase levels were first started with small bowel (duodenum) biopsy sampling at the time of endoscopy, along with the routine gastrointestinal biopsy procedure. These small bowel tissue samples were sent to a commercial corporation Joli Diagnostic, Inc (Williamsville, NY), where the measurement of lactase levels, together with the other disaccharidases determination of the small bowel biopsies, were all performed. The reference range of tissue lactase was 24.5 ± 8.0 units with abnormal defined as <15.0 units. One unit is defined by 1 μM/min/g protein.

Statistical analyses were performed by a statistician (JZ) and the team. Analysis of variance was performed to evaluate overall differences in lactose concentrations measurements of lymphocytic colitis, followed by post hoc pairwise comparisons (Tukey method). A scatter plot of age vs. lactose concentrations was drawn for lymphocytic colitis and colonic lymphocytosis (Fig. 2).

Results

The detailed clinical pathological data are summarized in Tables 1 and 2.

Ten cases of lymphocytic colitis cases were collected in total. The patient age range was 2–18 years, with mean age at 10.2 years. Female to male ratio was 7:3. Nine of the ten patients were Caucasian, and one was of another race (Moroccan). All ten patients presented with diarrhea and three also reported abdominal pain. One patient had joint pain at the same time, one had vomiting.

Colon endoscopy showed that a majority cases had normal appearance; only one case also had edema. Other abnormalities, such as nodular duodenum bulb or stomach, were also seen. Histological review gave us the following information. In the nodular duodenum bulb case, sections showed unremarkable small bowel mucosa consistent with duodenum; long, slender mucosal villi were well represented in the sections, and there was no increase in lymphocytes within the villous epithelium; one of the biopsies included a benign mucosal lymphoid follicle. For the edema and nodular stomach case, chronic inactive gastritis was identified; however, both special stain and immunostain for *Helicobacter pylori* appeared to be negative but the background stain was high. The case was in fact discussed at the time among pathologists and later with clinicians and it was felt two things needed to be ruled out. Number one, the colonic lymphocytosis could represent an epiphenomenon of *H. pylori* infection. Number two; this could be an early manifestation of Crohn disease. But follow-up data had no indication of either, so we decided to keep this case as a true lymphocytic colitis case in our study.

In terms of associated past medical history and comorbidities, noticeable ones included carpal tunnel syndrome, Down syndrome, and Hirschsprung disease; two patients carried the diagnosis of juvenile idiopathic arthritis. Positive family history in these patients was remarkable for autoimmune diseases including lupus, immune thrombocytopenic purpura/antithrombin antibody, diabetes mellitus, psoriasis, arthritis, and thyroid disease.

Most interestingly, eight out of ten patients (80%) had low lactase levels consistent with lactase deficiency. Among them, in addition to lactase deficiency, one patient had low amylase and lipase on pancreatic enzyme stimulation test and one patient had alpha glucosidase deficiency. Two other patients also had borderline lactase level. As shown in Table 3, compared to the control group of colonic lymphocytosis, the duodenal lactase concentrations [mean (standard deviation), μM/min/g protein] of lymphocytic colitis [9.04 (5.53)] were lower than those of colonic lymphocytosis [37.6 (16.1)], and this association of lactase deficiency and lymphocytic colitis is statistically significant ($P < 0.0001$). A scatter plot of age vs. lactase concentrations was drawn for lymphocytic colitis and colonic lymphocytosis to illustrate this difference (Fig. 2). It displays striking differences in lactase concentrations between lymphocytic colitis and colonic