

## Increasing duodenal intraepithelial lymphocytosis found at upper endoscopy: time trends and associations

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**Background:** Increased intraepithelial lymphocytosis (IEL) with preserved villous architecture is a common yet nonspecific finding on duodenal biopsies.

**Objective:** To study the change in frequency of isolated IEL on duodenal biopsy over time and determine whether previously reported disease associations have changed during that period.

**Design:** Retrospective study.

**Setting:** Single tertiary-care referral center.

**Patients:** Adults with a duodenal biopsy that showed normal villi and increased number of intraepithelial lymphocytes.

**Intervention:** Duodenal biopsy. Comprehensive electronic medical record search from January 1, 2000 through December 31, 2010.

**Main Outcome Measurements:** Demographic and clinical information.

**Results:** Of the 15,839 duodenal biopsies performed during the study period, 1105 (7.0%) had the histologic finding of interest. The odds of finding newly diagnosed celiac disease (CD) decreased by 0.9 on average during each year, whereas the odds of finding a non-celiac association increased by 1.12 times each year. Isolated increased IEL attributed to nonsteroidal anti-inflammatory drug (NSAID) use and small-intestine bacterial overgrowth (SIBO) increased by 1.06 and 1.3 times, respectively, for each year on average.

**Limitations:** Retrospective design, single center.

**Conclusion:** During the years 2000 through 2010, there has been an increased frequency with which duodenal biopsies were noted to have isolated increased IEL. The odds of a diagnosis of CD accounting for this finding have been decreasing, whereas the odds of NSAID use and SIBO have been increasing. Although the finding of isolated increased IEL on duodenal biopsy warrants work-up for CD in all patients, further investigation for other possible causes, including NSAID use and SIBO, should be considered as well. (*Gastrointest Endosc* 2014;80:105-11.)

*Abbreviations:* CD, celiac disease; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; IEL, intraepithelial lymphocytosis; NSAID, nonsteroidal anti-inflammatory drug; SIBO, small-intestine bacterial overgrowth.

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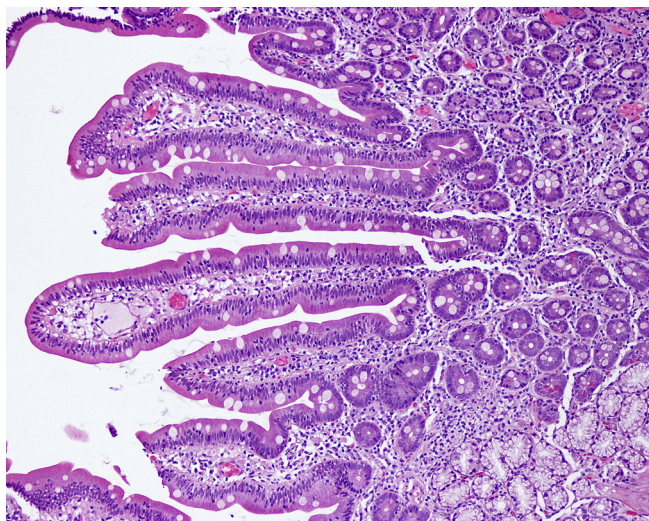
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**Figure 1.** Well-oriented villi without blunting. Intraepithelial lymphocytes are increased to 40 intraepithelial lymphocytes/100 epithelial cells (H&E, orig. mag.  $\times 100$ ).

Increased intraepithelial lymphocytosis (IEL) with normal villous architecture is a nonspecific finding on duodenal biopsies and one that appears to be reported with increased frequency. This histologic finding is equivalent to the early grade 1 lesion of the Marsh classification of celiac disease (CD) and may be the most sensitive marker for gluten ingestion in those patients.<sup>1,2</sup> Other reported associations of this histologic finding in adults include *Helicobacter pylori* infection, inflammatory bowel disease (IBD), small-intestine bacterial overgrowth (SIBO), enteric infections, autoimmune diseases, and nonsteroidal anti-inflammatory drug (NSAID) use.<sup>3-5</sup> Given the clinical associations that have been made with increased IEL, this finding can be problematic for clinicians who are left to decide how aggressive the evaluation should be to explain the noted histology. Although both retrospective and prospective studies have been done in an attempt to provide an algorithmic approach to these patients, the studies have been done on small samples and have not reflected the temporal change in frequency of this finding or its disease associations.<sup>6,7</sup>

From 1971 until 2005, increased IEL was defined as  $>40$  lymphocytes/100 epithelial cells<sup>8</sup> (Fig. 1), but the working definition changed in mid-decade to  $>30$  lymphocytes/100 epithelial cells<sup>9,10</sup>; the effect of this definitional change on the reported frequency of the histologic diagnosis has not been previously studied.

The aims of our study were to evaluate the change in frequency of isolated IEL on duodenal biopsy from 2000 through 2010, assess whether the new definition of increased IEL has resulted in a significant change in reporting of this histologic finding over time, and determine whether the previously reported disease associations have changed over the same time period. We hypothesized

### Take-home Message

- The finding of isolated increased intraepithelial lymphocytosis on duodenal biopsy has become more frequent. The odds of a diagnosis of celiac disease to account for this histologic finding have decreased, and the odds of nonsteroidal anti-inflammatory drug use and bacterial overgrowth to account for this histologic finding have increased.
- Clinicians should be mindful of non-celiac disease causes of isolated intraepithelial lymphocytosis on duodenal biopsy.

that the frequency of duodenal isolated IEL had increased over time and that increasing rates of new diagnoses of celiac disease accounted for this finding.

### METHODS

This study was approved by the Mayo Clinic Institutional Review Board. We searched the Mayo Clinic electronic pathology database from January 1, 2000 to December 31, 2010 for patients aged  $>18$  years who had the terms *normal villi* and *increased intraepithelial lymphocytes* in their duodenal biopsy reports. During the study period, our standard approach was to obtain 4 biopsy specimens, each through separate biopsy passes, from the postbulbar duodenum when there was an indication or a request for duodenal biopsy specimens; at that time, routine biopsies of the duodenal bulb were not performed. One pathologist with expertise in GI pathology reviewed all cases to confirm that villous architecture was preserved and that there were  $>30$  intraepithelial lymphocytes/100 epithelial cells.

All biopsy specimens had been fixed in formalin, embedded in paraffin, and cut at 4 microns for staining with hematoxylin and eosin. Routine sectioning protocol calls for 2 ribbons of tissue on each of 2 slides, giving approximately 16 levels of tissue available for review on each patient, optimizing the potential for finding well-oriented pieces. Until 2005, the working definition of duodenal intraepithelial lymphocytosis was  $>40$  lymphocytes/100 epithelial cells, but in 2005 our pathologists adjusted their practice in response to the recommendation that 30 lymphocytes/100 epithelial cells should be considered the upper limit of normal.

The medical records were reviewed for demographic information and for conditions associated with increased IEL. The latter assessment was done in a sequential fashion, beginning with known cases of CD and IBD and proceeding as shown in Figure 2. In patients with multiple possible associations, this resulted in a somewhat arbitrary choice for the “category” in which to place the patient, but all possible associations for any given patient were recorded and separately analyzed. The demographic and clinical

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