Duodenal lymphocytosis with no or minimal enteropathy: much ado about nothing?

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Duodenal lymphocytosis is a nonspecific finding that is being detected with heightened frequency. Although increased intraepithelial lymphocytosis with normal villous architecture classically corresponds to grade 1 of the Marsh classification, many other conditions have been reported to be associated with this histologic pattern. In this article, we offer a broad review of the associations of isolated increased intraepithelial lymphocytosis with celiac and nonceliac gluten sensitivity, as well as of the broadening nonceliac etiologies. *Modern Pathology* (2015) 28, S22–S29; doi:10.1038/modpathol.2014.135

The clinical presentation of gluten-sensitive enteropathy (GSE) has changed. More patients are diagnosed with less severe symptoms, and up to 40% are clinically silent.¹ Anemia is a common finding in 8% of patients, whereas there is a decrease in the number of patients presenting with the classic symptom of diarrhea (43% now compared with 73% before 1993).¹ In fact, many patients may be misdiagnosed, with 5–30% of patients having been at some point diagnosed with irritable bowel syndrome.^{2,3}

Duodenal lymphocytosis, that is, the increase of lymphocytes in the villous epithelial lining, has been debated in the literature over the last few years. During the last two decades, this diagnosis has been made with increasing frequency. This may have resulted from several converging dynamics. One is the recognition of an atypical presentation of GSE, including a preclinical stage that may present with minimal duodenal lymphocytosis; second, easier access to and increased use of some drugs (for example, NSAIDs) has been underscored;⁴ another is increased scrutiny from pathologists, which may have led to overinterpretation of duodenal lymphocytosis. However, in this review, we will attempt to clarify the diagnostic issues related to duodenal lymphocytosis and provide practical clues to direct the appropriate diagnosis and management of patients.

Normal Villus Architecture and Intraepithelial Lymphocyte Count

The gastrointestinal tract, with its large surface area and population of plasma cells, T and B lymphocytes, macrophages, and dendritic cells, is the largest lymphoid organ of the human body. Although most cellular components of the immune mucosal system rest in the lamina propria, the limited intraepithelial lymphocytes (IELs) are particularly significant, as they are the first cells to interact with any harmful luminal antigen, either infectious or alimentary. In the duodenum, the vast majority of IELs are phenotypically CD8+ T cells expressing α/β T-cell receptors on the surface.⁵

Practically, whether evaluating the villous architecture or counting IELs, it is best not to assess biopsies that are not well oriented, as tangential sections can produce an artificial impression of increased IELs (and architectural abnormalities). Specifically, this may lead to inappropriate counting of lymphocytes adjacent to but located below the epithelial basement membrane and therefore in the lamina propria. This pitfall is particularly true when immunohistochemistry is used (see below). Thickness of the section is important as well, and it has been suggested that accurate evaluation requires well-oriented 3- to 4- μ sections.^{6,7}

The upper limit of IELs in the normal proximal small bowel previously was considered to be 40/100 epithelial cells. However, this figure was based on counts performed on jejunal capsule biopsies, where IEL counts inherently are higher than in the duodenum.⁸ In more recent studies utilizing thin-cut sections and endoscopically obtained biopsies, several authors have shown the upper limit of

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normal for the duodenum to be 20–25 IELs/100 epithelial cells.^{6,7} It also has been emphasized that a greater density of IELs is seen in the crypts and, normally, a decrease in number from the base toward the tip is noted.⁹ Consequently, counting IELs at the tips of the villi and observing a lack of decrescendo from crypts to tips have been recommended as the most useful method of confirming an increase (Figure 1).^{9,10}

Some authors have suggested that CD3 and CD8 immunohistochemistry can facilitate the detection of IELs, particularly as some lymphocytes can have an irregular nuclear outline mimicking granulocytes, and others could be mistaken for epithelial cell nuclei.¹¹ It has been suggested that when immunohistochemistry is used, the upper limit of normal be increased to 30 per 100 IELs⁶ before being considered pathologic. However, not all pathologists have found these additional stains helpful, cautioning that they decrease the sensitivity derived from appreciating a loss of the normal IEL decrescendo pattern.¹²

Causes of Increased IELs in Architecturally Normal Duodenal Biopsies

Given the location and proposed role of IELs, it is no surprise that the number of IELs can increase because of a variety of immunologic stimulants, whether by an ingested or endogenous antigen or via autoimmune causation. In fact, duodenal lymphocytosis once has been observed in between 1.3%¹³ and 2.2%¹⁴ of patients undergoing upper GI tract endoscopy and small intestinal biopsy, and has been increasingly noted in up to 7% over the last 11 years in a single-center study of 15 839 duodenal biopsies.⁴ However, it remains a vexing diagnostic problem, as a specific etiology is never discovered for many cases of duodenal lymphocytosis.^{13–16} (Tables 1 and 2) Nevertheless, a well-constructed report should emphasize a certain number of recognized associations to initiate a proper and timely clinical workup.

It should be stressed that a diagnosis of duodenal lymphocytosis does not represent a diagnosis of GSE, and, alternatively, a diagnosis of Marsh grade 1 lesion (that is, normal architecture with preserved crypt to villi ratio and increased IELs) applies only to patients with proven gluten-sensitive enteropathy (see below).

Gluten-Sensitive Enteropathy

Approximately 11% of patients with duodenal lymphocytosis test positive for IgA endomysial antibodies or antitissue transglutaminase, and one-third have the DQ2 allele associated with celiac disease. The prevalence of GSE in architecturally normal small intestinal biopsies and duodenal lymphocytosis has been reported to be 9–40%.^{13,14,17} Various terms are used in the

Figure 1 Normal duodenal villus. Only a few scattered lymphocytes are noted, well below 20 lymphocytes/100 epithelial cells.

literature to describe these patients: gluten sensitivity with mild enteropathy, latent celiac disease, and potential celiac disease.¹²

It has been reported that an even distribution of IELs along the villi, and thus a loss of the normal decrescendo pattern from base to tip of villi, is more likely to be associated with GSE than other etiologies.^{9,10,13,18} It is, however, a feature neither specific nor sensitive for gluten-related disorders (Figure 2).^{9,13}

The use of immunohistochemistry is debated. It has been reported as helpful in highlighting the presence of increased IELs and the loss of decrescendo.^{11,12} However, the improved diagnostic specificity supported by some^{11,12,18} has been contested by others.¹⁹

It is important to note that these patients, even if presenting with mild morphological changes, can

Table 1 Causes of proximal small intestinal intraepithelial lymphocytosis with normal villus architecture

Gluten-related disorders (celiac disease, nonceliac gluten sensitivity, wheat allergy)
Non-gluten food hypersensitivity (for example, cereals, cow's milk, soy products, fish, rice, and chicken)
Infections (for example, <i>Giardia</i> , <i>Cryptosporidia</i> , <i>H. pylori</i> , tropical sprue)
Bacterial overgrowth
Drugs (for example NSAIDs)
Immune dysregulation (for example, Hashimoto's thyroiditis, rheumatoid arthritis, SLE, and so on)
Immune deficiency (for example, IgA deficiency, CVID)
Inflammatory bowel disease (CD/UC)
Lymphocytic and collagenous colitis
GVHD
Preinfiltrative intestinal T-cell lymphoma
Idiopathic (including irritable bowel syndrome)

develop nutritional deficiencies leading to iron deficiency anemia and osteoporosis.^{20,21}

For many years, small intestinal biopsies, supplemented by serological tests, have been held to be the gold standard of diagnosis of GSE. However, the optimal diagnostic sensitivity and specificity, as well as the high positive predictive value of IgA antihuman tissue transglutaminase and IgA endomysial antibody immunofluorescence, have led some to consider that histopathologic confirmation may not always be necessary in a subset of *pediatric* patients.²² However, the situation is different in Marsh type 1 injury pattern, since it is well established that the likelihood of a positive test correlates with the degree of mucosal injury, and GSE cases with intraepithelial lymphocytosis alone can often have antibody titers in the normal range.^{23–25} Thus, negative serology does not exclude a diagnosis of GSE with a Marsh type 1 pattern (that is, normal architecture with preserved crypt to villi ratio and increased IELs); a morphologic evaluation remains relevant.

Testing for HLA DQ haplotype is a mainstay of the diagnostic armamentarium. However, its usefulness is limited; a negative result makes a diagnosis of celiac disease very unlikely, but a positive test does not establish a diagnosis, in the context of duodenal lymphocytosis, because the DQ8/DQ2 haplotypes are seen in 25–40% of the general population.^{25,26} As other genes are believed to have a role in the development of GSE, many clinicians resort to a trial of gluten-free diet, or sometimes, a gluten challenge followed by rebiopsy.

Nonceliac Gluten Sensitivity

Despite being consistently testing negative for celiac disease serology, some individuals can develop a variety of symptoms related to wheat and/or gluten ingestion. Those with positive immunoglobulin E-mediated tests are diagnosed with wheat allergy; the others are considered to suffer from *nonceliac*

Table 2 Prevalence of conditions associated with duodenal intraepithelial lymphocytosis

	Kakar ¹³ (n = 43)	Mahadeva ¹⁴ (n = 14)	Hammer ¹⁶ (n = 100)	Shmidt ³⁶ (n = 48)	Aziz ¹⁵ (n = 100)
Celiac disease	9%	21%	18%	19%	16%
Tropical sprue	1%	—	1%	—	—
<i>H. pylori</i> gastritis	—	—	6%	6%	14%
Bacterial overgrowth	5%	—	3%	—	—
NSAIDs	14%	—	8%	20%	21%
IBD	12%	—	8%	11%	2%
Autoimmune conditions	14%	—	6%	—	4%
Unexplained	7%	21%	26%	33%	34%
IBS	9%	14%	20%	—	—
Other	28%	43%	4%	11%	9%

Figure 2 In this example, the increase of intraepithelial lymphocytes is particularly noticeable at the tips of the villi. This patient was eventually noted to have elevated IgA tissue transglutaminase.

gluten sensitivity. In all, the symptoms are alleviated when wheat and gluten are excluded from the diet.²⁷

The prevalence of nonceliac gluten sensitivity has been between 0.55 and 6% of the population. This wide range may indicate confusion in correctly classifying patients; the lack of validated diagnostic tests for an accurate estimation; and/or selection bias. Its pathogenesis remains unclear, and the presenta-

tion includes a combination of IBS-like symptoms (for example, bloating, abdominal pain, diarrhea, and/or constipation), and systemic manifestations (for example, headache, fatigue, and anemia).^{27–29}

The diagnosis of nonceliac gluten sensitivity is made by excluding GSE. Morphologically, it is not associated with villous blunting. However, whereas some authors state that the absence of histologic alterations is an essential diagnostic parameter, others have reported a high frequency of duodenal lymphocytosis (90%), sometimes associated with increased eosinophilic infiltrate.^{28,30} Colonic biopsies also may reveal an infiltration of the epithelium and lamina propria by eosinophils (although the architecture is preserved) in about two-thirds of the patients.³⁰ Alternatively, increased colonic IEL infiltration is noted in only 25% of the patients. Importantly, these cells are T-cell receptor-alpha/beta IELs, whereas T-cell receptor-gamma/delta IELs are only noted in GSE.²⁹

Hypersensitivity to Other Alimentary Proteins

Hypersensitivity to non-gluten components of foods such as gluten-free cereals, cow's milk, soy products, fish, rice, and chicken has been associated with duodenal lymphocytosis in some affected patients. Variable degrees of villous alteration with crypt hyperplasia can be seen. Reported diagnostic clues include increased eosinophils and other clinical manifestations of an allergic phenotype.^{31–34} Duodenal lymphocytosis in autistic children, whether or not associated with the lactase deficiency frequently recorded in these patients, also has been observed.³⁵

Infections

In 6–14% of cases, duodenal lymphocytosis is associated with *Helicobacter pylori* gastritis.^{15,16,36} The increased IELs usually display a patchy distribution in the proximal duodenum. Another diagnostic clue is obviously the detection of chronic active gastritis with *H. pylori* organisms. Furthermore, a subset of these cases resolves when the infection is eradicated.^{36–38} Tropical enteropathy (sprue), which may present with normal villi but increased IELs, is diagnosed in patients who have lived in tropical regions, even for a limited time. The morphology is identical to that of celiac disease (Figure 3). However, the detection of severe ileal involvement (if biopsied) will be helpful in considering this condition. Increased eosinophils are also a noted histologic clue in the appropriate clinical setting.³⁹ Tropical sprue is suspected to be caused by chronic infection by enteric enterogenic coliform.³⁹ This hypothesis is confirmed indirectly by a temporal relationship to bouts of acute diarrhea and a good response to a variety of antibiotics, vitamin B12, and folate therapy. Parasitic infections

Figure 3 Tropical sprue in an immigrant from Southeast Asia. Notably, no marked eosinophilic infiltration is detected. Jejunal biopsies, clinical suspicion, and negative serology will help to rule out celiac disease.

such as *Giardia lamblia* and *Cryptosporidium* also can be associated with increased lymphocytic exocytosis (Figure 4). Careful review of the epithelial lining will be critical to the diagnosis of these etiologies. Common eosinophilia is reported but may not always be a distinctive feature. Elevated IEL counts also can be seen post-viral enteritis,^{40,41} although some degree of villous atrophy is usually recognized (Figure 5). In such cases, appropriate clinical communication is obviously cardinal to establish a timeline between the suspected viral episodes and the intestinal symptomatology.

Bacterial overgrowth, whether related to gastric hypochlorhydria or intestinal dysmotility, has been associated with an increase in IELs (in the absence of villous atrophy) compared with control biopsies.⁴² However, only some cases in that study had an IEL density above what is currently considered the normal range. In the study by Kakar *et al*,¹³ two cases (4.5%) of intraepithelial lymphocytosis were related to bacterial overgrowth (Figure 6). Conditions causing stagnation or recirculation of the intestinal contents are predisposing factors. Associated conditions include anatomic abnormalities (diverticula, anastomosis, and stricture), anomalies of motility (for example, diabetic neuropathy), as well as a multifactorial condition (chronic pancreatitis and irritable bowel syndrome).

Figure 4 Cryptosporidiosis with intraepithelial lymphocytosis. The parasite is easily detectable adhering to the apex of epithelial cells (arrowhead).

Drugs

NSAIDs have been noted in frequent association with duodenal lymphocytosis, with their use reported in 14–29.5% of patients.^{4,13} It is hypothesized that increased use in preventive care (for example, cardiology) and liberal access account for the increased incidence in the association. In a recent study, Brown *et al*³⁹ found that 20% of patients taking a proton pump inhibitor had elevated IELs. The relative hypochlorhydria with bacterial overgrowth having a role in that setting could be hypothesized. However, this was not confirmed recently by Schmidt *et al*.⁴ Recently, it has been recognized that olmesartan, an angiotensin II receptor antagonist, can lead to significant lymphocytic exocytosis; however, it is commonly associated with various degrees of blunting.⁴³

Autoimmune Conditions

It is not unexpected that disorders of immune regulation can be associated with elevated IELs and various degrees of villous atrophy. This was the case

Figure 5 Example of post-viral intraepithelial lymphocytosis in a patient with a very suggestive clinical history. Furthermore, celiac serology was negative, and no increased intraepithelial lymphocytes were present on two subsequent biopsies.

Figure 6 Bacterial overgrowth is commonly associated with increased intraepithelial lymphocytes. However, only a few cases show distinct increase such as this one demonstrates. Although the histology is not characteristic, clinical information (for example, older age, small-bowel diverticula, pancreatitis, and so on) may steer the differential diagnosis appropriately.

Figure 7 Crohn's disease. Numerous intraepithelial lymphocytes are evident along the entire length of the villi. The patient was TTG- and HLA-DQ2-negative, and also had active ileitis at the time of biopsy.

in 14% of patients in the series by Kakar *et al*¹³ who had an immune dysregulation condition. Reported conditions include Hashimoto's thyroiditis, Grave's disease, rheumatoid arthritis, psoriasis, multiple sclerosis, and systemic lupus erythematosus.^{8,13} Intestinal intraepithelial lymphocytosis in the setting of glomerulonephritis is also reported, particularly when presenting with nephrotic syndrome.⁴⁴

Increased IELs in the proximal small intestine often are detected in patients with hypogammaglobulinemia, whether because of IgA deficiency or common variable immunodeficiency.⁴⁵ Villous atrophy can be mild. Morphologic clues to the diagnosis can include reduced numbers of plasma cells, frequent parasitic infection (for example, *Giardia*), glandular apoptosis, and lymphoid follicle formation.⁴⁶

Chronic idiopathic inflammatory bowel disease can be associated with duodenal intraepithelial lymphocytosis.^{12,13,47} Duodenal intraepithelial lymphocytosis also has been noted in association with both lymphocytic and collagenous colitis. Notably, in many cases, the association appears to be exclusive of gluten sensitivity, despite the recognized association of both variants of microscopic colitis with celiac disease.^{48–50}

Interestingly, the finding of duodenal intraepithelial lymphocytosis in patients with Crohn's disease can be observed concurrent with full-blown active disease but may also precede active Crohn enteritis (Figure 7).¹²

Graft versus host disease also, although uncommonly, can display prominent numbers of IELs.⁵¹ The finding of epithelial cell apoptosis and some degrees of architectural disturbance together with a distinct clinical setting allows for correct diagnosis.

Autoimmune Enteropathy

This is a rare condition characterized by severe and protracted diarrhea with weight loss from malabsorption and immune-mediated changes to intestinal mucosa. This disorder generally occurs among infants and young children, although some cases have been reported in adults. Small intestinal histopathology usually encompasses various degrees of villous atrophy, lymphoplasmacytic infiltration of the lamina propria, and crypt hyperplasia. Cases with preserved architecture result from early diagnosis or successful therapy. However, IELs are more numerous in crypts than in the surface and remaining villus tips. There is also usually marked crypt damage with apoptosis.⁵²

Neoplasias

Type 2 refractory celiac disease (RCD type 2) is a known precursor lesion of enteropathy-associated T-cell lymphoma. The morphology is of a minimally or non-atrophic small intestinal mucosa. Special studies will be diagnostic, as they demonstrate a clonal population of IELs with an abnormal phenotype. RCD type 2 ought to be considered in the diagnosis of duodenal lymphocytosis in the setting of known celiac disease patients who lack histologic and/or clinical improvement despite prolonged gluten-free diet.⁵³

Intraepithelial Lymphocytosis Without Definitive Diagnosis

In many cases, the detection of duodenal intraepithelial lymphocytosis may not lead to a recognizable specific etiology. This category represents between 7 and 34% of the cases diagnosed.^{13–16,36} Some of these patients meet clinical criteria for irritable bowel syndrome and may respond symptomatically to a gluten-free diet. Whether these patients have a subtle form of gluten sensitivity remains uncertain, although there is some experimental support for this suggestion.⁵⁴

Conclusions

Up to 2.5% of proximal small intestinal mucosal biopsies display increased IELs (> 25 IELs/100 IELs) in the absence of villous architectural change. In most cases, this is because of immunological activation of the lymphocytes that are normally resident in the epithelium. The causes for this increase in number of IELs are multiple and include reactions to intraluminal antigens and small intestinal

manifestations of autoimmune or other allied diseases. Gluten-related disorders are the most common cause, accounting for 9–40% of cases.^{13,14,17} The establishment of a diagnosis of celiac disease and other gluten-related disorders can be clinically difficult and relies on a weighted assessment of clinical, serological, and histopathological data. Pathologists can help by highlighting cases that have a uniform distribution of IELs over the villus length as being more likely to represent gluten sensitivity than those showing increased numbers but in a persisting decrescendo pattern.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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