Coeliac disease and other intraepithelial lymphocytic disorders of the upper gastrointestinal tract

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Summary

The finding of increased intraepithelial lymphocytes (IELs) in the upper gastrointestinal (GI) tract is common to a wide variety of disorders that involve mucosal injury. Coeliac disease, or gluten-sensitive enteropathy, is perhaps the first entity in pathologists' differential diagnosis when asked to identify disorders with increased IELs, but it is far from the only condition that can result in such a finding. The numerous causes that can result in this histological feature can be easily organized into three categories. Inflammatory and immune causes include coeliac disease and other autoimmune conditions, as well as relatively rare haematolymphoid neoplasms. Infectious causes include numerous conditions that often have subtle histological findings, such as giardiasis and bacterial overgrowth. Finally, 'ingested' causes range from pharmacological agents to morbid obesity, which has also been associated with the isolated finding of increased IELs in the upper GI tract. This review focuses on selected entities from each of these categories, with special attention to coeliac disease.

Keywords bacterial overgrowth; coeliac disease; enteropathy-type T-cell lymphoma; giardiasis; gluten-sensitive enteropathy; inflammatory bowel disease; tropical sprue

Introduction

Increased intraepithelial lymphocytes (IELs) are commonly encountered in the practice of any pathologist who reviews gastrointestinal (GI) biopsies. Many duodenal biopsies are submitted for diagnosis with express instructions from our clinical colleagues to 'rule out sprue' or 'rule out coeliac disease'. While a significant increase in IELs accompanied by architectural changes can be highly suggestive of certain pathological conditions when accompanied by appropriate clinical information, what is more often encountered—and much more often a source of frustration—is a questionable or low-level increase in lymphoid cells with intact architecture. Often, the clinical history is not at all intact, which adds to the potential confusion.

Pathologists asked to name conditions that feature increased IELs are likely to place coeliac disease first on the list and, indeed, IELs are the fundamental histological lesion in this disease, so they must be carefully sought. In reality, however, increased IELs are a 'final common pathway' in numerous disorders that injure the mucosa of the gut; thus, they are quite non-specific on their own and may be found in a wide variety of situations.

Disorders involving the GI tract that have increased IELs as a major feature can be easily organized into three categories. The first, *inflammatory and immune* causes, contains many of the most familiar and memorable conditions, such as gluten-sensitive enteropathy (GSE), other autoimmune diseases and inflammatory bowel disease. *Infectious* aetiologies, such as giardiasis, must be actively and carefully sought in biopsy specimens, because the histological findings can be very subtle. Finally, '*ingested*' causes include a range of substances that can be introduced from outside the GI tract, such as pharmacological agents and foods to which the patient may be hypersensitive.

Guidelines exist for what constitutes an increase in IELs in the GI tract. In the small intestine, particularly the duodenum, a fairly large population of IELs can be considered normal; generally, there are no more than 30 or 40 IELs for every 100 enterocytes under normal conditions, or fewer than 12 lymphocytes at the tip of any villus.[1,2] The number is much smaller in the stomach, where generally no more than 5–6 IELs are seen for every 100 epithelial cells.[3]

Inflammatory/immune diseases

Gluten-sensitive enteropathy

Perhaps more commonly known by a variety of other names, including coeliac disease, coeliac sprue, non-tropical sprue and gluten-induced enteropathy, GSE is a fairly common affliction in North America and Europe, where it affects as many as 1 in every 120 people.[4] The fundamental issue in GSE is a cell-mediated immune response to a dietary protein (gluten) that is found in a surprising variety of foods, beverages and even medications containing wheat, barley, rye or derivatives thereof.[5] Clinical and serological [serum antibodies to gliadin and tissue transglutaminase (TTG)] findings are integral to the diagnosis of coeliac disease, because similar histological features can be seen in a variety of conditions, as suggested earlier. A resolution of the patient's symptoms when gluten-containing substances are removed from the diet is the final component of the clinicopathological diagnosis.

Patients with GSE usually complain of diarrhoea at presentation, reflective of nutrient malabsorption that results from mucosal damage due to the inflammatory process.[6] In children, the malabsorptive condition can result in growth retardation and 'failure to thrive'.[4,7] If not diagnosed early, this may result in permanent short stature, delay of puberty and more specific manifestations of nutrient deficiency, such as megaloblastic anaemia, vitamin K deficiency with coagulopathy, or rickets. Iron deficiency is commonly encountered because of the significant mucosal damage that can occur in the proximal small intestine, where iron is primarily absorbed. In fact, unexplained iron-deficiency anaemia is the most common presenting sign in adult patients with GSE, of whom as many as half may not have significant diarrhoea.[4,8,9] While adult patients with GSE may exhibit signs of undiagnosed childhood disease, such as short stature, the disease can also have its onset primarily in adulthood.[9]

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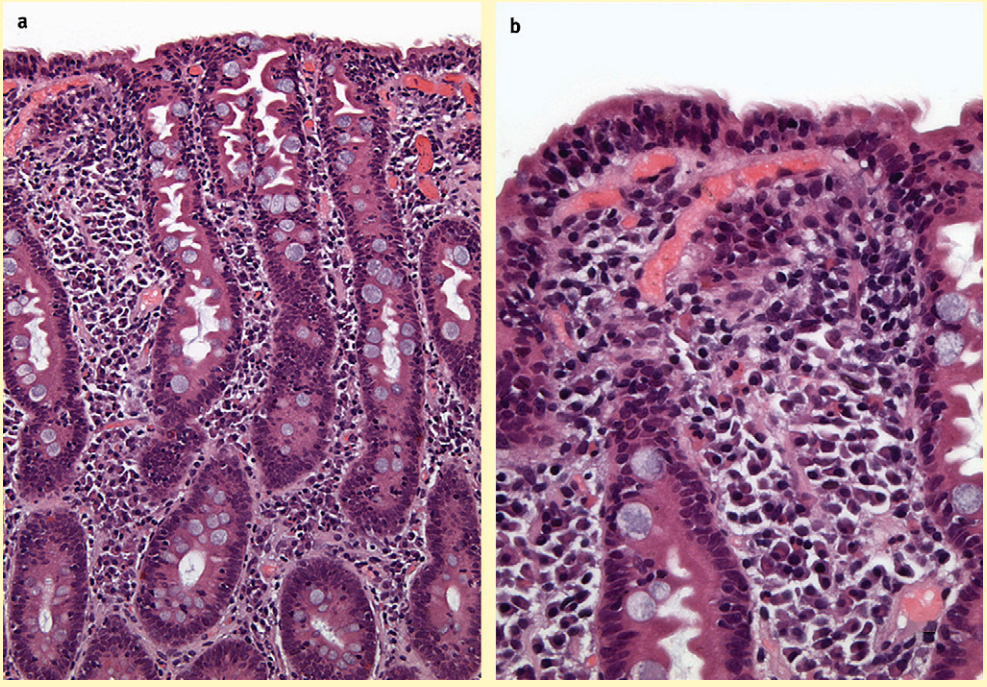
Although the diagnosis of GSE relies heavily on clinical information, mucosal biopsy, usually of the duodenum, remains the 'gold standard' diagnostic tool for the confirmation of clinical suspicion and serological findings.[4,10] Normal duodenal mucosa contains villi that are long and slender, with a length at least three times the depth of adjacent crypts. GSE classically results in 'blunting' of the villi, which subsequently appear short and stout.[11,12] Severe cases can result in total flattening of the mucosa (Figure 1). The loss of the villous component is accompanied by 'crypt hyperplasia'. As a result, the overall mucosal thickness remains essentially unchanged, but villous loss is compensated for by deepening of the crypt compartment. Crypt epithelium undergoes proliferation during this process, resulting in easily-visible ('high-riding') mitotic figures in the enterocytes of the superficial mucosa. These architectural changes in the mucosa are accompanied (or preceded) by an increase in the number of IELs (Figure 1), a manifestation of the immune character of the disease.[1,2] In large part, these are T cells (CD3 +), a high proportion of which carry the γδ T-cell receptor.[13] In some cases, IELs are the only visible manifestation of disease and the mucosal architecture is essentially intact, which makes the diagnosis more challenging. This is most often true early in the disease course and/or when there is partial treatment, and this subtle finding should be carefully sought in order to avoid overlooking an important manifestation of the disorder. While the proximal small intestine is most often affected, the changes can extend throughout the organ, although the distal findings are usually not as severe as those in the duodenum and proximal jejunum. In addition, increased IELs can be seen outside the small intestine, including the stomach (vide infra) and the colon.[11,14]

The desire for a standardized grading and reporting system for the histological findings in GSE is well-established, and the Marsh (or Marsh–Oberhuber) classification, which uses six categories, has been extensively utilized for this purpose since its description.[15,16] Recently, a simplified classification system has been proposed, which relies on three basic villous morphologies: 'A', non-atrophic; 'B1', atrophic with villous:crypt ratio <3:1; and 'B2', atrophic with villi no longer discernible.[17,18] These categories, in combination with an IEL count of >25 per 100 enterocytes, were found to have greater interobserver agreement than the Marsh classification in a recent study of 60 patients.[18] Interestingly, although improved, the mean kappa statistic (indicative of interobserver agreement) for the new system was still only moderate (0.55) versus fair (0.35) for the Marsh classification. At our institutions, we use the phrases 'partially developed' or 'fully developed sprue-type changes' depending on the degree of villous blunting/atrophy. These histological findings can then be correlated with the clinical and serological data to complete the diagnosis.

Gliadin is an alcohol-soluble peptide portion of gluten. Antibodies to gliadin, as well as to TTG are the most commonly sought serological evidence for GSE.[5,8] Antibodies to the latter antigen are detected using an enzyme-linked immunosorbent assay (ELISA), and this method is considered the most sensitive test for diagnosis, although assay for the closely-related antiendomysial antibodies is still considered more specific.[19,20] The likelihood of serological positivity is correlated with the degree of tissue injury. In the presence of appropriate serological and histological findings, the final component in the diagnosis is resolution of symptoms and mucosal changes in response to a gluten-free diet (GFD). Histological improvement, such as decreased epithelial injury and fewer IELs, can be seen within the first few weeks of the institution of a GFD, and a long-term



a Low-power view of fully developed sprue-type changes. Note the elongated crypts with complete lack of villi. **b** High-power view showing damaged surface epithelium with large numbers of intraepithelial lymphocytes.

Figure 1