Sailing Past the Horizon

The Histologic Diagnosis of Celiac Disease in “Nonflat” Intestinal Mucosa

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When one reads about the histologic features of celiac disease in a textbook of surgical pathology, it is the absence of normal intestinal villi that generally is stressed as the key diagnostic feature. The features of a “flat mucosa,” in combination with elongation of the intestinal crypts, evidence of epithelial damage, and a variable increase in chronic inflammation of the lamina propria, form the histologic diagnosis of sprue. The alteration of villus architecture was deemed so central to the diagnosis of celiac disease that in the past it had been the practice of many institutions to include an examination of the villi in fresh small intestine biopsy specimens with a dissecting microscope before examination of histologic sections. However, just as Christopher Columbus sailed past an apparently flat horizon to help prove that the world is round, the time has come to broaden the horizons of the histologic diagnosis of celiac disease.

In the Western world, the major cause of sprue is celiac disease, which is an autoimmune disease triggered by antigens present in flour gluten. However, an established body of scientific and clinical literature states that the manifestation of this immune injury in the bowel covers a histologic spectrum, with only a subset of symptomatic gluten-sensitive patients displaying complete sprue changes. But as Goldstein and Underhill write in this issue of the Journal, “It does not seem to be common knowledge among United States pathologists that clinically significant GS [gluten sensitivity] can be associated with architecturally normal villi.” In fact, it now seems that perhaps the most important histologic aspect of gluten-sensitive enteropathy is an increase in the number of intraepithelial lymphocytes (IELs), with some experts in this field recommending a trial of gluten restriction in a symptomatic patient with this morphologic finding alone. However, much of this evidence has not been published in journals concerned with diagnostic histopathology, and many of these studies used morphometric analytic techniques too cumbersome for routine diagnostic use. This is why the study by Goldstein and Underhill is so valuable: it reaches the audience it needs to, with criteria that can be applied to routine histologic examination.

The Goldstein and Underhill study underscores the correlation of an increased number of IELs with serologic and clinical evidence of gluten sensitivity, even in biopsy specimens in which there is no appreciable decrease in villus height. Some words of caution are in order: just as not all intestinal sprue is caused by gluten sensitivity, not all small intestinal biopsy specimens showing increased IELs are due to gluten sensitivity. In fact, Goldstein and Underhill show that there is a substantial overlap of patients with and without gluten sensitivity with such a finding, although they found that the pattern of IEL distribution was a useful discriminator (see their article for details). Although the causes of increased IEL in the non–gluten sensitive patients were not identified in their article, the differential diagnosis includes sensitivity to other food antigens, infections, common variable immunodeficiency syndrome, and selective IgA deficiency.

If there is a risk of making the histologic diagnosis of celiac disease less specific, then why travel down this road? One answer is that with the increasing use of serologic tests (especially the detection of antiendomysial and antitransglutaminase autoantibodies) that have excellent sensitivity and specificity, there will be an ever-increasing demand for histologic confirmation of gluten sensitivity in patients in whom the classic microscopic appearance of flattened villi may not have fully developed. In this category are patients with dermatitis herpetiformis, who seem to have an alternative form of gluten sensitivity manifested primarily by...
dermatologic disease and who tend to have less severe forms of enteropathy. Since the histologic confirmation of intestinal injury remains a cornerstone in the diagnosis of this group of disorders, the underrecognition of these histologic changes by surgical pathologists may lead to diagnostic confusion. Also, the patient’s clinician may not be considering a diagnosis of gluten sensitivity, and the suggestion by the surgical pathologist of such a disorder can be a valuable service for establishing the correct diagnosis in gluten sensitivity, even in patients without full-blown sprue.

What terminology should we use for this group of disorders? While the term celiac disease is still in widespread use, other terms such as gluten sensitivity, gluten intolerance, and gluten-sensitive enteropathy are being used to describe this disorder. Because there seems to be an entrenched association of the histologic features of sprue with the term celiac disease, perhaps there should be a movement by histopathologists to the newer terminology of gluten-sensitive enteropathy. By adopting a new moniker unencumbered by the baggage of the old and more accurately describing the underlying etiologic features, new thinking may be stimulated that allows the widespread adoption of the histologic criteria of increased IELs in the diagnosis of these disorders.

The finding of increased numbers of IELs in the stomach and the colon has been referred to as lymphocytic gastritis and lymphocytic colitis. These findings also seem to not be caused by a single etiologic factor, and, in fact, both can be associated with gluten sensitivity. A similar terminology may be adopted for the small intestine, with the term lymphocytic enteritis used as a nonspecific histologic description of a pattern of injury. By using this approach, a pathologist may give a descriptive diagnosis if there is insufficient clinical information to confidently make a diagnosis of gluten-sensitive enteropathy. For example, a biopsy specimen that shows relatively normal villus architecture with a mean IEL count of 8 per 20 enterocytes and a uniform distribution of IELs along the length of the villi may be signed out as “lymphocytic enteritis suggestive of gluten-sensitive enteropathy” or, even more descriptively, “increased intraepithelial lymphocytes suggestive of gluten-sensitive enteropathy.” As with all “medical biopsies,” there is no substitute for good communication between pathologist and clinician in order to integrate the clinical, laboratory, and histologic findings for the most accurate classification of the patient’s disorder.

What to do with the rare patients who have sprue but do not respond to gluten withdrawal? After subtracting the patients who ultimately are shown to have lymphoma, the remainder are most commonly classified as having “refractory sprue” or “refractory celiac disease,” which also could lead to the unfortunate terminology refractory gluten sensitivity that may or may not be an accurate reflection of the underlying disease state. The preferred terminology would be idiopathic lymphocytic enteritis.

The more widespread recognition by histopathologists of the pattern of injury manifested by increased numbers of IELs in gastrointestinal biopsy specimens may spur additional studies or promote the association of this finding with other etiologic factors. I hope this recognition will not result in our dropping off a precipice into a realm of diagnostic confusion, but instead will allow us to sail over the horizon into a new age of discovery.

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References


