Top tips for the diagnosis of celiac disease

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1. **Order the right serologies.** Tissue transglutaminase (TTG) IgA has a high sensitivity and specificity for celiac disease, and is thus the key test to order. Because patients with selective IgA deficiency will not have an elevated TTG IgA (and because this population has a higher risk of celiac disease), the total IgA should also be measured. If the total IgA is undetectable, IgG serologies (TTG and deamidated gliadin peptide [DGP]) can be used, but their specificity is significantly lower. As such, elevations of TTG IgG or DGP IgG have a low positive predictive value for celiac disease, particularly if the total IgA is normal.

   Genetic testing for celiac disease susceptibility haplotypes (human leukocyte antigen DQ2 and DQ8) is useful primarily for its negative predictive value; that is, a negative result makes celiac disease very unlikely. Testing may be helpful in cases of family screening (so as to determine whether serial screening is necessary) or in patients who have already adopted a gluten-free diet. These haplotypes are common (present in approximately 40% of the population), the great majority of whom do not have celiac disease. Therefore, their positive predictive value for celiac disease is low, and genetic testing should not be routinely included on celiac disease testing panels.
2. **Perform an upper GI tract endoscopy if the tissue transglutaminase TTG IgA is elevated.** Although TTG IgA has a high specificity for celiac disease, it is imperfect and false positives occur. The treatment of celiac disease, a gluten-free diet, is a life-long prescription (at least until nondietary therapies arrive). As such, this diet should not be recommended without a firm diagnosis. The American College of Gastroenterology guidelines suggest using serologic criteria (a >10-fold TTG IgA elevation and a positive endomysial antibody) for a diagnosis of likely celiac disease among adults unwilling or unable to undergo upper endoscopy. However, this is considered an "after the fact" diagnosis. Evidence is emerging about whether a >10-fold TTG IgA elevation can be considered highly predictive of villus atrophy in a variety of patient populations and laboratories. While we await this evidence, upper endoscopy with duodenal biopsy is still recommended.
3. **Even if celiac disease is not top-of-mind, consider performing a biopsy of the duodenum during upper endoscopy.** Celiac disease can present with a variety of signs and symptoms that can include iron deficiency anemia, weight loss, and abdominal pain. The cost-effectiveness of routine duodenal biopsy during upper endoscopy depends on the underlying prevalence of celiac disease in the particular population. If the patient has recent negative celiac serologies and does not have multiple risk factors for celiac disease (such as a family history or concurrent autoimmune disease including type 1 diabetes or Addison disease), it is reasonable to skip a duodenal biopsy. But if the serologic status is unknown, taking biopsy specimens of the duodenum may often be appropriate.

   Although there are several characteristic endoscopic findings in the duodenum that are suggestive of celiac disease, a sizable proportion of patients with celiac disease have a normal-appearing duodenum on endoscopy (Fig. 1A and B). As such, a normal appearance does not obviate the need to perform a biopsy.
4. **Take enough biopsy specimens.** Villus atrophy can be patchy in patients with celiac disease, and the sensitivity of duodenal biopsy for the detection of villus atrophy is directly correlated with the number of specimens submitted. Patients with normal duodenal biopsies who are subsequently found to have villus atrophy often had suboptimal sampling initially. About 4 to 6 pieces of tissue should be submitted for histopathology, and this should include the duodenal bulb. Although previously thought to be low yield because of distortion by Brunner glands, the bulb may be the only part of the small intestine with villus atrophy in a patient with celiac disease. Up to 10% of newly diagnosed patients have so-called "ultra short" celiac disease where histologic abnormalities are confined to

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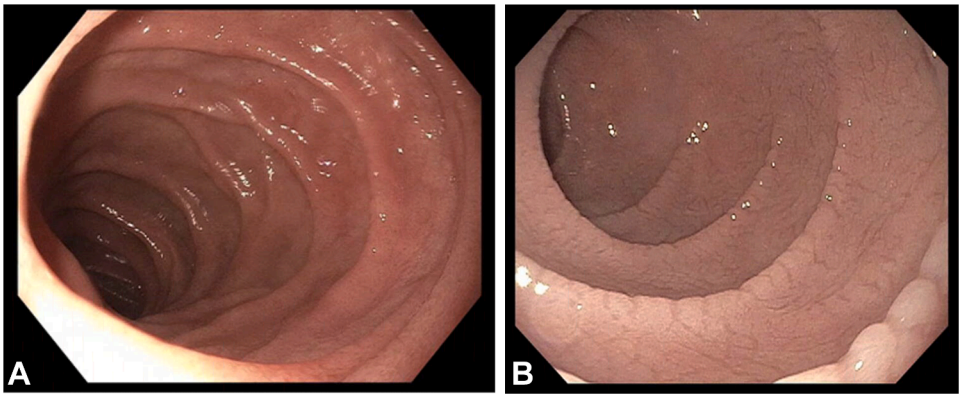

Figure 1. Endoscopic appearance of the distal duodenum in celiac disease. This can range widely and may be normal (**A**) or exhibit fissuring and scalloped folds (**B**). These 2 patients had similar histology (partial villus atrophy) on biopsy despite differing endoscopic findings.

the bulb. These patients tend to be younger and may have less severe symptoms. The duodenal bulb is the site where gluten is at its highest concentration in the small bowel, which likely accounts for its being most sensitive to villus damage.

5. **Maximize proper "orientation" of the biopsy specimens.** Measurement of villus architecture requires well-oriented specimens. Although most pathology laboratories do not incorporate manual orientation of specimens before embedding, this practice can improve measurement of villus height. Short of that, taking 1 bite per pass of the biopsy forceps has been shown to improve the chances of well-oriented specimens. Variability of orientation is another reason that submitting more specimens has a higher diagnostic yield.
6. **Biopsy the stomach.** Although the histopathologic hallmark of celiac disease resides in the duodenum, gastric pathology may affect interpretation. The finding of duodenal intraepithelial lymphocytosis with normal villus architecture (Marsh 1 histology) is a nonspecific finding, although it sometimes represents early celiac disease. In this scenario in particular, gastric histology may be helpful, because gastric mucosal inflammation (such as *Helicobacter pylori* gastritis) can cause this finding. Lymphocytic gastritis, an uncommon clinical entity that can be seen in patients with celiac disease, can sometimes contribute to symptoms and may be missed if the stomach is not sampled (Fig. 2).
7. **Inspect the esophagus.** Patients with celiac disease have an increased risk of eosinophilic esophagitis (EOE). The endoscopic findings of EOE can be subtle, and a proper inspection of the esophagus with a low threshold to perform a biopsy is appropriate, so as not to miss this condition that can sometimes be diagnosed concurrently.
8. **Ask about the patient's diet leading up the endoscopy.** The sensitivity of duodenal biopsy for the detection of villus atrophy in celiac disease is dependent on whether the patient is still eating gluten regularly. Some patients, particularly those who were found to have an elevated TTG IgA and have been waiting for their endoscopy, may have adopted a gluten-free diet months before their endoscopy. Others may be on a low-gluten diet (such as a low FODMAP [fermentable oligosaccharides, disaccharides, monosaccharides, and polyols] diet) to manage gastrointestinal symptoms. The duration of gluten challenge can range from 2 weeks to more than 3 months, and this is often determined by the patient's willingness to ingest gluten for an extended period. A longer challenge increases diagnostic sensitivity. The diet of the patient, including the duration of the gluten-free diet or gluten challenge,

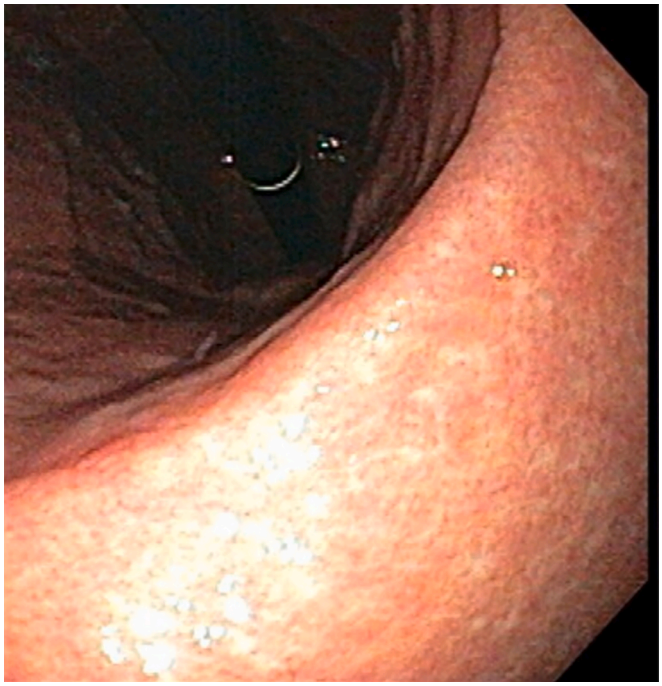

Figure 2. Diffuse gastric erythema in a patient whose histology exhibited lymphocytic gastritis.

should ideally be included in the endoscopy report to aid in interpretation of the biopsy results.

9. **Get to know your pathologist.** The histologic findings of celiac disease can be subtle and can be affected by the patient's diet. Reviewing borderline or discrepant biopsy results with an expert GI pathologist can often illuminate the situation. The pathologist can comment on specimen quality and orientation, degree of suspicion for celiac disease, and alternative diagnoses, which can sometimes be hinted at based on histologic features.
10. **Consider alternative diagnoses for duodenal villus changes.** If a patient's duodenal biopsy shows villus atrophy suggestive of celiac disease, but a TTG IgA has not yet been measured, it is critical to confirm the diagnosis by checking a TTG IgA before advising a gluten-free diet. If the TTG IgA is elevated, the celiac disease diagnosis is confirmed. But if it is normal, alternative diagnoses need to be considered. These include tropical sprue, common variable immunodeficiency, HIV enteropathy, giardiasis, and other causes. Seronegative celiac disease, as well as celiac disease with elevated gliadin antibodies but negative TTG IgA, are additional possibilities. Before assuming that the diagnosis is celiac disease and thus urging a lifelong gluten-free diet with incomplete data, confirm with a TTG IgA.

DISCLOSURE

The author disclosed no financial relationships.

Registration of Clinical Trials

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