

# Educational Case: Immune-Related Disorders of the Bowel: Celiac Disease

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*The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289517715040>.*

## Keywords

pathology competencies, organ system pathology, gastrointestinal tract, immune-related disorders of the bowel, celiac disease, collagenous sprue, villous blunting, serologic studies

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## Primary Objective

*Objective GT5.2: Celiac Disease.* Explain the pathophysiology of gliadin hypersensitivity (celiac disease).

Competency 2: Organ System Pathology; Topic GT: Gastrointestinal Tract; Learning Goal 5: Immune-Related Disorders of the Bowel.

## Patient Presentation

A 30-year-old otherwise healthy woman presents with malodorous diarrhea of 6 months' duration. It is sometimes associated with abdominal cramps and bloating. It has been getting worse in the past month, and she also reports a 10-pound weight loss and chronic fatigue. She is a frequent traveler and experienced diarrhea during a trip to Canada last summer, which resolved within a few days. She denies nausea, vomiting, constipation, dark stool, or blood in stool. The patient is lactose intolerant, but denies consuming lactose containing dairy products in past 6 months. She has not changed her diet in any other way. She is not taking nonsteroidal anti-inflammatory drugs (NSAIDs) or any other over-the-counter medications. No one else in her family has similar symptoms. She has a cousin with Crohn disease. Physical examination reveals no fever. The

abdomen is soft, nontender and nondistended, without masses or organomegaly. The bowel sounds are normal.

## Diagnostic Findings, Part I

The patient's primary care physician ordered some screening tests. Complete blood count revealed hemoglobin 11.8 g/dL (reference range 14.0–17.4 g/dL) and mean corpuscular volume 76 fL (reference range 80.0–96.0 fL). Iron level was 30 µg/dL (reference range 65–175 µg/dL). The stool occult blood, culture, and ova and parasite tests were negative. Liver function tests and fecal calprotectin (a marker for intestinal inflammation and surrogate marker of inflammatory bowel disease) were within normal ranges. Serum immunoglobulin A (IgA), IgG, and IgM levels were within normal ranges.

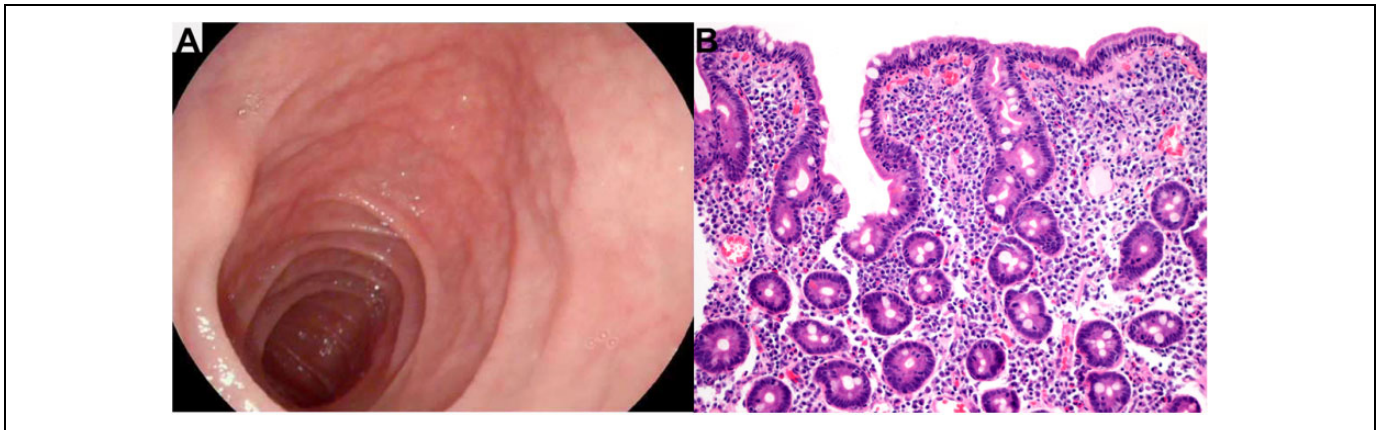
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**Figure 1.** A, Endoscopic view of duodenal mucosa. B, Duodenal biopsy (hematoxylin and eosin stain; original magnification: 20 $\times$ ).

### Questions/Discussion Points, Part 1

#### *What Diseases Would You Consider in Your Differential Diagnosis?*

Since the patient is a frequent traveler, and she has a medical history of lactose intolerance and family history of Crohn disease, chronic parasitic infection, food sensitivities, and inflammatory bowel disease are important considerations. Other common differential diagnoses for chronic diarrhea include celiac disease, chronic viral or bacterial infections, irritable bowel syndrome, microscopic colitis, autoimmune enteropathy, and primary immunodeficiency. However, the foregoing initial screening results make infection, inflammatory bowel disease, and immunodeficiencies unlikely explanations for her symptoms.

### Diagnostic Findings, Part 2

Further autoimmune workup revealed anti-tissue transglutaminase (anti-TTG) IgA >128 U/mL (reference range <10 U/mL), anti-deamidated gliadin peptide (anti-DGP) IgA > 142 U/mL (reference range <10 U/mL), and anti-DGP IgG >302 U/mL (reference range <10 U/mL).

### Questions/Discussion Points, Part 2

#### *How do the Additional Laboratory Findings Help You Narrow the Differential Diagnosis?*

The above serology results make celiac disease highly likely. Screening for IgA anti-TTG antibodies is the first-line test for celiac disease. This may be performed in conjunction with serum IgA levels since patients with selective IgA deficiency may have false negative TTG results. The presence of IgA-endomysial antibodies (EMA) supports the diagnosis in patients with equivocal TTG titers.<sup>1</sup> Assays for IgG-TTG, IgG-DGP, and IgG-EMA are available for IgA deficient patients, a group at increased risk for development of celiac disease.

Serologic studies display suboptimal specificity for celiac disease. Elevated anti-TTG and anti-EMA alone are insufficient to diagnose this disorder, and biopsy confirmation is required.<sup>2</sup> Furthermore, a small percentage of patients with negative serologies prove to have celiac disease.<sup>3</sup> This may occur in patients with primary immunodeficiencies (eg, common variable immunodeficiency, selective IgA deficiency), those on therapeutic immunosuppression, or early in the disease course. Seronegativity was recently described in patients with severe, long-standing disease in whom anti-TTG antibodies were bound to the small intestinal mucosa and sequestered from circulation.<sup>4</sup> At present, serology is considered a diagnostic modality, whereas endoscopic duodenal biopsy represents the gold standard.

#### *What Is Recommended Next for Evaluation of This Patient?*

The patient was referred to a gastroenterologist for upper gastrointestinal endoscopy evaluation. The gastric mucosa appeared normal endoscopically. The duodenal endoscopy and biopsy findings are shown in Figure 1.

### Diagnostic Findings, Part 3

#### *What Are the Abnormalities Present in Figure 1? What Are the Possible Explanations of the Histologic Findings in Figure 1B?*

Figure 1A shows mildly scalloped mucosa in the second portion of the duodenum. This alteration is common in patients with celiac disease. Figure 1B shows a duodenal biopsy sample (hematoxylin and eosin stain) displaying partially effaced villous architecture, increased intraepithelial lymphocytes and hyperplastic crypts. While these histologic findings suggest celiac disease, by themselves they are insufficient to distinguish celiac disease from its mimics, as discussed subsequently. However, based on the positive serologic studies and characteristic histologic features, a diagnosis of celiac disease

was rendered in the case at hand. The patient was put on gluten-free diet. After 8 weeks, the symptoms improved substantially.

### Questions/Discussion Points, Part 3

#### *What Is the Pathophysiology of Celiac Disease?*

Celiac disease is an allergic response to dietary gluten in genetically susceptible individuals. Gluten is partially digested into a mix of complex proteins, including gliadins and glutenins, by intestinal enzymes. Gliadins cause increased intestinal permeability by binding to the CXCR3 chemokine receptor on enterocytes and causing release of zonulin, which transiently weakens intercellular junctions. Undigested peptides leak into the lamina propria where they are further broken down by tissue transglutaminase. Resultant deaminated gluten fragments may be recognized as pathogens, in some individuals, and presented to CD4+ T cells by human leukocyte antigen (HLA) DQ2/8-bearing antigen presenting cells.<sup>5</sup> This activates Th2 cells and leads to B cell proliferation and Th1-mediated cytokine release. Inflammation-mediated damage to the intestinal epithelium allows passage of more gluten fragments into the mucosa and incites a self-sustaining inflammatory response.<sup>6</sup> Elimination of dietary gluten is the only effective treatment.

#### *What Genetic Features Are Associated With Celiac Disease?*

Patients with celiac disease often harbor HLA DQ2 and DQ8 alleles. In fact, HLA genotyping may be used as a screening test for children at risk for celiac disease.<sup>7</sup> Absence of these alleles essentially excludes the diagnosis, particularly in asymptomatic patients. The risk of celiac disease is 1 in 10 for first-degree relatives of affected patients, a substantial increase over the 1% prevalence observed in the United States population.<sup>8,9</sup>

#### *Which Other Disorders Are Associated With Celiac Disease?*

Patients with Down syndrome, Turner syndrome, and those with other immune-mediated disorders, such as autoimmune thyroid disease and type 1 diabetes are at increased risk for celiac disease. Patients with celiac disease frequently have extraintestinal manifestations. Iron deficiency anemia results from inadequate iron absorption in the duodenum.<sup>10</sup> Dermatitis herpetiformis is a blistering skin disease which is associated with celiac disease.<sup>11</sup> Peripheral neuropathy and ataxia may result from impaired small intestinal uptake of vitamin B12 and folate. Osteoporosis and infertility are also associated with gluten sensitivity.<sup>1</sup>

#### *What Would You Expect to See in Endoscopic Biopsy Samples From the Duodenum?*

The normal duodenal mucosa displays circumferential folds called “plicae circularis” that are oriented perpendicular to the

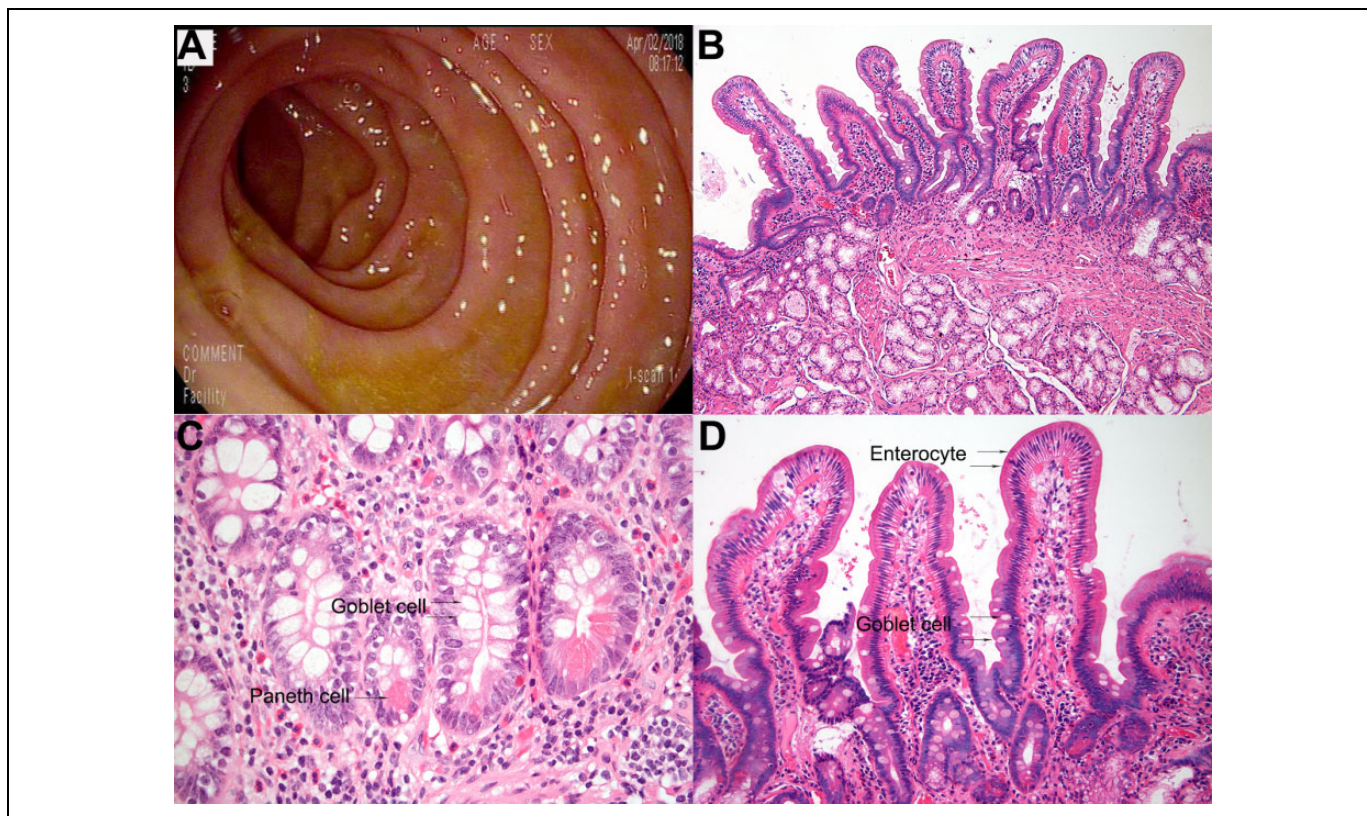
long axis of the small intestine; these facilitate absorption of ingested nutrients (Figure 2A). Histologically, the mucosa is organized into villous projections with a core of lamina propria lined by absorptive cells and goblet cells and downward extensions of epithelium between villi, called crypts (Figure 2B). The crypts are lined by similar epithelia, as well as Paneth and endocrine cells (Figure 2C). The normal villous to crypt ratio is approximately 3-4:1. Intraepithelial CD8+ T cells normally number approximately 20 per 100 enterocytes, or 1 T lymphocyte per 6 enterocytes.<sup>12</sup> They display a “decrescendo pattern” of distribution, meaning that their density is lower at the villous tips compared to crypt bases (Figure 2D). The lamina propria also contains abundant plasma cells and lymphocytes and occasional neutrophils and eosinophils.

Small intestinal samples from patients with celiac disease display varying degrees of intraepithelial lymphocytosis, villous shortening/blunting, increased lymphoplasmacytic lamina propria inflammation, and crypt hyperplasia. Early or milder cases of celiac disease may display normal villous architecture and only increased intraepithelial lymphocytes (Figure 3A and B). Better-developed cases show markedly shortened or completely effaced villi (Figure 3C), elongated and hyperplastic crypts (Figure 3D), and lamina propria expansion by chronic inflammation (Figure 3D). Although occasional intraepithelial neutrophils may be present, this is not a prominent feature of celiac disease.

#### *What Disorders Are in the Histologic Differential Diagnosis of Celiac Disease?*

Other disorders such as peptic duodenitis, tropical sprue, common variable immunodeficiency, autoimmune enteropathy, and small intestinal Crohn’s disease share histologic features with celiac disease, namely villous blunting and intraepithelial lymphocytosis. Peptic duodenitis typically occurs in the setting of gastric *Helicobacter pylori* infection or reactive gastropathy due to NSAIDs or other gastric irritants. Intraepithelial lymphocytes are only minimally increased and foveolar metaplasia of the surface epithelium is almost uniformly seen. Tropical sprue is a rare disorder that is thought to be due to an unidentified microbe. It displays all of the features of celiac disease, although they may be more pronounced in the ileum compared to the duodenum.<sup>13</sup> Patients with common variable immunodeficiency have markedly decreased levels of circulating immunoglobulins, and biopsy samples throughout the gastrointestinal tract may display a decrease or absence of plasma cells.<sup>14</sup> Autoimmune enteropathy is more common in young males who may have circulating autoantibodies to goblet cells or parietal cells. Biopsy samples may also display loss of goblet cells or parietal cells.<sup>15</sup> Finally, Crohn disease is characterized by abnormal chronic (lymphocytes, plasma cells) and active (neutrophil-rich) intestinal inflammation, and architectural remodeling. Non-necrotic epithelioid granulomas are the most helpful diagnostic findings, but this feature is inconsistently present.





**Figure 2.** Normal duodenal mucosa. A, Endoscopic view of normal duodenum with smooth mucosa and circumferential intestinal folds (plicae circulares). B, Normal duodenal mucosa with slender villi and villus to crypt ratio of 3-4:1, and underlying submucosal Brunner's glands (hematoxylin and eosin stain; original magnification: 10 $\times$ ). C, High power view of duodenal crypts showing goblet cells and Paneth cells (hematoxylin and eosin stain; original magnification: 40 $\times$ ). D, Normal duodenal villi with scattered intraepithelial lymphocytes more prominent in the base (hematoxylin and eosin stain; original magnification: 20 $\times$ ).

### What Is the Natural History of Celiac Disease?

The vast majority of patients experience resolution of signs and symptoms of celiac disease shortly after gluten withdrawal. Only 1% to 2% experience refractory celiac disease defined as persistent or recurrent symptoms despite adherence to gluten-free diet for 6 to 12 months. Refractory celiac disease comprises 2 subgroups; intraepithelial T cells display normal coexpression of CD3 and CD8 in type 1 refractory celiac disease, whereas CD8 expression is lost in type 2 disease.<sup>16</sup> The latter group is at risk for progression to enteropathy-associated T-cell lymphoma, an aggressive malignancy with <20% five-year overall survival.<sup>17</sup> The risk of intestinal lymphoma is 6 to 7-fold higher in patients with celiac disease compared to the general population.<sup>18</sup> So-called "collagenous sprue" is a pattern of injury that may be seen in refractory celiac disease (Figure 4), but can also be seen in patients with hypersensitivity to other dietary proteins or, rarely, as a hypersensitivity reaction to angiotensin II receptor antagonists.<sup>19</sup> Thus, this pattern is not necessarily indicative of gluten sensitivity and patients with the finding of collagenous sprue may or may not benefit from gluten withdrawal. Patients with long-standing, untreated celiac disease are at more than 4-fold increased risk for small intestinal

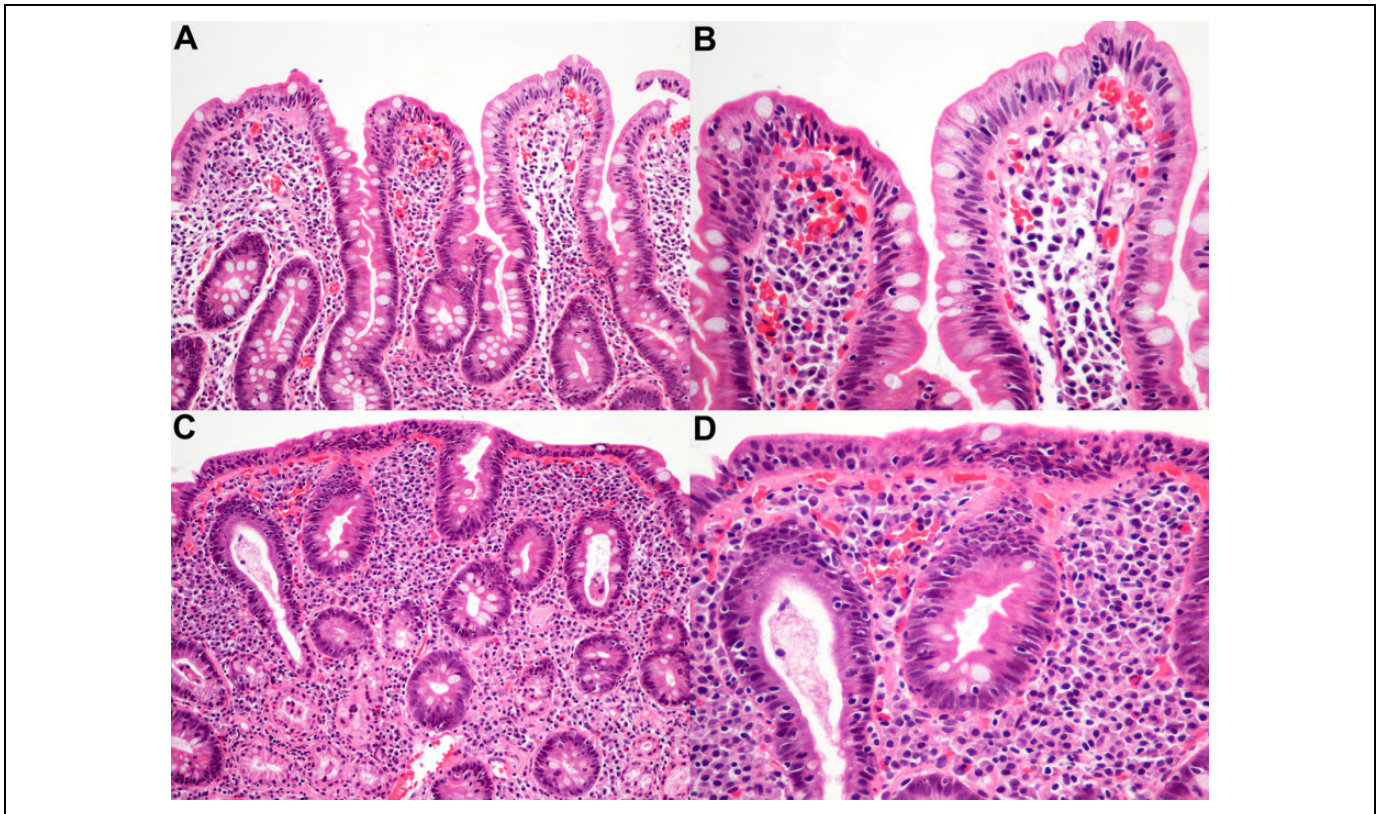
adenocarcinoma.<sup>20</sup> Although the mechanism of carcinoma development is incompletely understood, recent studies suggest a role for mismatch repair deficiency in these cases.<sup>21</sup>

### What Is the Role of Gluten-Free Diet on the Treatment of Celiac Disease?

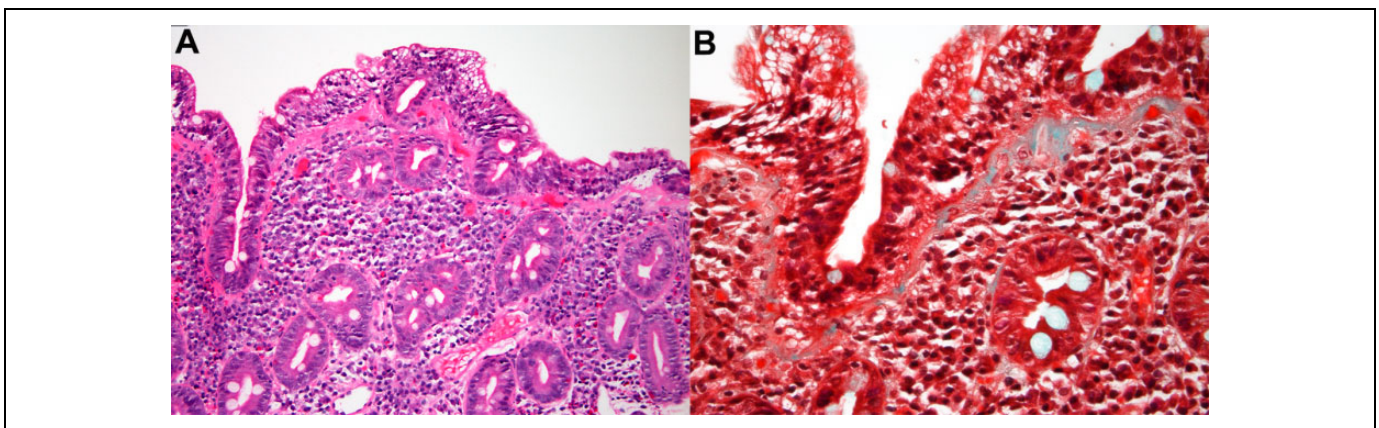
At present, gluten-free diet is the only effective treatment for celiac disease. Gluten-free diet is a diet that strictly excludes gluten, a composite of storage proteins termed prolamins and glutelins found in wheat, barley, rye, oat, and other related grains. Strict adherence to the gluten-free diet can help to meet the therapeutic goals in almost all patients with celiac disease. However, adhering to a gluten-free diet is challenging, especially for young adults. Many factors including cultural background, social isolation, financial burden of purchasing gluten-free foods, and incorrect/lack of food labeling have contributed to the nonadherence. Regular dietetic follow-up and utilization of gluten-free food database can be helpful to improve adherence.<sup>22,23</sup>

Adoption of gluten-free diets and consumption of gluten-free foods have risen substantially in the United States over the past 3 decades.<sup>24</sup> This is due, in part, to increased awareness of celiac disease. Elimination of gluten and wheat from the diet





**Figure 3.** Celiac disease. A and B, Celiac disease with mild villous blunting and increased intraepithelial lymphocytes particularly in the villous tips (hematoxylin and eosin stain; original magnification: A, 20 $\times$ ; B, 40 $\times$ ). C and D, Celiac disease with almost completely blunted villi, marked intraepithelial lymphocytosis, hyperplastic crypts, and expanded lamina propria by chronic inflammation (hematoxylin and eosin stain; original magnification: C, 20 $\times$ ; D, 40 $\times$ ).



**Figure 4.** Collagenous sprue. A, Duodenal mucosa with typical features of celiac disease and irregularly thickened subepithelial collagen (hematoxylin and eosin stain; original magnification: 40 $\times$ ). B, A trichrome stain highlighting the thick and irregular subepithelial collagen with entrapped capillaries (original magnification 40 $\times$ ).

alleviates gastrointestinal symptoms in some individuals who do not have celiac disease. These groups are now said to have nonceliac gluten sensitivity and nonceliac wheat sensitivity, respectively.<sup>25,26</sup> Emerging evidence suggests that avoidance of gluten may benefit patients with certain psychiatric disorders, atopic diseases, endometriosis, and fibromyalgia.<sup>24</sup>

The gluten-free lifestyle is also gaining popularity among healthy individuals. Although gluten avoidance may contribute to weight loss, other health benefits have not been convincingly shown. Indeed, some evidence suggests that gluten-free diets exacerbate cardiovascular disease by reducing intake of beneficial whole grains.<sup>27</sup>

## Teaching Points

1. Celiac disease is a multifactorial disorder that demonstrates the interplay between genetic and environmental factors in immune-mediated diseases.
2. The diagnosis of celiac disease relies upon serologic evaluation of increased antibodies against TTG, EMA, and DGP; duodenal biopsy confirmation of villous shortening/blunting; intraepithelial lymphocytosis; crypt hyperplasia; and clinical evaluation of patient's response to gluten-free diet. This underscores the importance of interdisciplinary communication in the management of gastrointestinal disorders.
3. Like many gastrointestinal disorders, celiac disease has extraintestinal manifestations related to immune dysregulation, such as dermatitis herpetiformis, and nutritional deficiencies such as iron-deficiency anemia.
4. Celiac disease displays a spectrum of histologic abnormalities ranging from normal mucosal histology and villous architecture, to mild intraepithelial lymphocytic infiltration and partial villous atrophy, to marked lymphocytosis and total villous blunting, related to disease duration and severity.
5. Recognition of celiac disease is clinically important since gluten withdrawal is the only effective therapy, and untreated disease can lead to potentially serious sequelae including severe malnutrition, lymphoma, and adenocarcinoma.

## Declaration of Conflicting Interests

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