Clinical and Histologic Mimickers of Celiac Disease

Amrit K. Kamboj, MD1 and Amy S. Oxentenko, MD2

Celiac disease is an autoimmune disorder of the small bowel, classically associated with diarrhea, abdominal pain, and malabsorption. The diagnosis of celiac disease is made when there are compatible clinical features, supportive serologic markers, representative histology from the small bowel, and response to a gluten-free diet. Histologic findings associated with celiac disease include intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy, and a chronic inflammatory cell infiltrate in the lamina propria. It is important to recognize and diagnose celiac disease, as strict adherence to a gluten-free diet can lead to resolution of clinical and histologic manifestations of the disease. However, many other entities can present with clinical and/or histologic features of celiac disease. In this review article, we highlight key clinical and histologic mimickers of celiac disease. The evaluation of a patient with serologically negative enteropathy necessitates a carefully elicited history and detailed review by a pathologist. Medications can mimic celiac disease and should be considered in all patients with a serologically negative enteropathy. Many mimickers of celiac disease have clues to the underlying diagnosis, and many have a targeted therapy. It is necessary to provide patients with a correct diagnosis rather than subject them to a lifetime of an unnecessary gluten-free diet.

Clinical and Translational Gastroenterology (2017) 8, e114; doi:10.1038/ctg.2017.41; published online 17 August 2017

Subject Category: Review

CELIAC DISEASE

Celiac disease (CD) is an autoimmune condition characterized by sensitivity to gluten, a protein found in wheat, barley, and rye.1 In the United States, 0.71% of the population has CD, with highest prevalence in whites and females.2 Although 0.63% of the American population follows a gluten-free diet, the majority of these individuals do not have CD.2 In fact, most cases of CD are undiagnosed.2 The prevalence of CD is increasing in developing countries.3

A combination of immune, genetic, and environmental factors play a role in the development of the disease. In CD, gliadin, a component of gluten, reaches the small intestine and triggers an inflammatory response characterized by villous atrophy and inflammatory cell infiltration of the epithelium and lamina propria.1 In patients that develop CD, human leukocyte antigen (HLA)-DQ2 (~95% of cases) or HLA-DQ8 (~5% of cases) genetic alleles must be present; however, these alleles are also present in 30–40% of the general population.1 Environmental factors such as breastfeeding may be protective, while rotavirus infection may promote disease development.4,5

Clinical features of CD vary by age group. Young children may manifest with diarrhea and abdominal distention; older children can present with short stature, neurological symptoms, and anemia; adults classically have diarrhea and abdominal pain, but may present with extra-intestinal features, such as iron-deficiency anemia and premature metabolic bone disease.1 Diarrhea is becoming less common as a presenting feature, and the diagnosis is being increasingly made in asymptomatic or at-risk populations.6 The diagnosis of CD is made using a combination of clinical, serologic, and histologic findings. Serological testing is often performed in patients with unexplained abdominal discomfort, chronic diarrhea, laboratory test abnormalities (vitamin or mineral deficiencies), premature metabolic bone disease, family history of CD, or a personal history of other autoimmune disorders.1 The initial screening test for CD is immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) antibody, except in patients with known or suspected IgA deficiency, in which case an IgG-based serology is required.3 Upper endoscopy with duodenal biopsies remains the gold standard for diagnosis, and should be performed in all adult patients when serological testing is positive, and in patients with strong features of CD despite negative serologies.1 Duodenal biopsies classically demonstrate intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy, and a chronic inflammatory cell infiltrate in the lamina propria (Figure 1a,b).1 Patients with CD should exhibit resolution of symptoms when started on a gluten-free diet.1 As outlined above, the absence of HLA-DQ2 and HLA-DQ8 alleles effectively rules out the disease.

A gluten-free diet forms the cornerstone of management in patients with CD, with elimination of wheat, barley, and rye.1 Oats are generally safe in patients with CD, although there may be a small risk of oat cross-contamination or contact with gluten-containing food products; most patients with CD are allowed to ingest oat products unless they present with severe clinical features, in which case oats may be held initially. After a new diagnosis of CD is made, all patients should be referred

1Department of Internal Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA and 2Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA
Correspondence: Amy S. Oxentenko, MD, Department of Internal Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA. Email: oxentenko.amy@mayo.edu
Received 27 May 2017; accepted 2 July 2017
weight loss, which can be seen in many gastrointestinal conditions, the extra-intestinal features of CD broadens the number of conditions that may clinically mimic CD.

Irritable bowel syndrome (IBS) is the most commonly diagnosed gastrointestinal disorder, and has features that mimic CD. Symptoms include abdominal pain along with altered bowel form and/or frequency. IBS is often associated with other disorders including somatic comorbidities. The ROME IV criteria is often used to diagnose IBS and requires recurrent abdominal pain on average at least one day per week for the last 3 months associated with two or more of the following: related to defecation, change in frequency of stool, and change in form or consistency of stool. Symptoms need to be present for at least 6 months. Before a diagnosis of IBS is made, alarm features need to be assessed, and consideration should be given to test for CD in those with a diarrhea-predominant or mixed-type pattern. Functional diarrhea is similar to IBS, yet without abdominal pain, and may also clinically mimic CD.

Small intestinal bacterial overgrowth (SIBO) is known to cause diarrhea, bloating, and weight loss, which may mirror symptoms of classic CD; SIBO may also be a cause of recurrent or refractory symptoms in a patient with known CD. Patients may have carbohydrate, protein, or fat malabsorption, and deficiencies in iron, vitamin B12, and fat-soluble vitamins, which may occur, in part, due to intraluminal damage from proliferating bacteria. In healthy individuals, several physiological mechanisms exist that serve to limit bacterial growth and SIBO occurs when these protective mechanisms fail. While no universal definition of SIBO exists, the gold standard remains a small bowel aspirate demonstrating 10^5 or more colony forming units per milliliter of bacteria grown. The treatment of SIBO consists of managing any underlying diseases, correcting nutritional deficiencies, and use of antibiotics.

Autoimmune and/or inflammatory conditions such as inflammatory bowel disease (IBD), microscopic colitis, thyroid dysregulation, and adrenal insufficiency may all cause clinical features that mimic CD, or be concurrently present in patient known to have CD. IBD occurs when the intestinal microbiome triggers an inappropriate inflammatory response, and while there is a genetic susceptibility to IBD, the pathogenesis is multifaceted. While individuals can be affected at any point in life, the disease typically occurs in those 15 to 30 years of age. Although Crohn’s disease can affect any part of the gastrointestinal tract, it most commonly involves the terminal ileum. Given the small bowel involvement with Crohn’s disease, clinical features may mimic CD with abdominal pain, diarrhea, weight loss, and features of malabsorption. The treatment for Crohn’s disease is complex and individualized, and involves lifestyle modifications (smoking discontinuation, if applicable, and NSAID avoidance), medical management with varying degrees of immunomodulatory or immunosuppression therapy, and occasionally surgical intervention.

Infectious mimickers include giardiasis and both viral and bacterial gastroenteritis, although most viral and bacterial infections are self-limited and do not cause the chronic symptoms that can be seen with Giardia infection, unless post-infectious IBS ensues. Other chronic parasitic infections may also cause symptoms that mimic CD. Other less common...
clinical mimickers include tropical sprue, autoimmune enteropathy, drug-induced enteropathy, Whipple’s disease, and others that will be discussed in more detail below.

While there are some patients who have celiac-like symptomatology, and others who have celiac-like histology on small bowel biopsies, some conditions can mimic both clinical and histologic features of CD, leading to diagnostic challenges in this group of patients. Given the large number of clinical celiac mimickers, the remainder of the review will focus on the histologic mimickers of CD.

HISTOLOGIC MIMICKERS OF CD

The characteristic histologic features of CD include partial or total villous atrophy, crypt hyperplasia, increased tip-predominant intraepithelial lymphocytes (IELs), lymphocyte and plasma cell infiltrate in lamina propria, and normal CD3+/CD8+ infiltrates. The modified Marsh-Oberhuber classification (Table 1) can be used to classify the histologic features associated with CD. In this scheme, IELs, architecture, and the degree of villous blunting are used to categorize lesions into types 0–4. Type 3 and higher is associated with increased IELs, hyperplastic crypts, and villous blunting, and is more often seen in symptomatic CD. Histologic features such as mucosal erosions, neutrophilic infiltrates, non-tip-predominant IELs, loss of goblet or plasma cells, crypt abscesses, and loss of CD8 expression are uncharacteristic of CD.

EARLY HISTOLOGIC MIMICKERS

Early histologic mimickers of CD can be defined as those conditions causing increased IELs with no villous atrophy, and crypts that are normal or have minimal hyperplasia (Figure 2a, b, Table 2). Prior to 2005, the “normal” number of IELs in the small bowel was defined as 6–40 lymphocytes per 100 epithelial cells. However, recent studies highlight that the upper limit of normal for lymphocyte count from duodenal biopsies is 25 per 100 epithelial cells, and from 2005 onward, many pathologists define greater than 25–30 lymphocytes per 100 epithelial cells as abnormal. The difference in the upper limit of normal IELs over time may be secondary to the use of jejunal biopsies in older studies, and the fact that some studies have based counts on anti-CD-3 staining, which is not used routinely in clinical practice.

The histologic finding of isolated IELs (also referred to as lymphocytic duodenitis) has been associated with a number of clinical conditions, and is becoming increasingly noted. In one large single-center study, an analysis of 15,839 duodenal biopsies from 2000 to 2010 in adult patients revealed that 1,105 (7%) cases reported the finding of isolated IELs with normal architecture. While the finding of isolated IELs was present in 3% of cases in 2000, it was noted in nearly 11% of cases by 2010. Moreover, during this time period, the odds of a CD diagnosis decreased by 0.9 annually, while the odds of a non-CD diagnosis increased by 1.1 annually. CD was found in only 6.8% of patients with isolated increased IELs in the duodenum and normal villi architecture, when patients with known CD were excluded. In addition to this large study, three other smaller studies (N = 14–100 patients) similarly reported the etiologies for isolated IELs in the duodenum to be from known or newly diagnosed CD (9–21%) or IBD (2–12%), non-steroidal anti-inflammatory drug (NSAID) use (14–21%), SIBO (5–9%), autoimmune conditions (4–14%), or “other” (9–43%), with 7–34% of cases of the IELs being unexplained.

Increased lymphocytic duodenitis has also been reported in children. The etiologies for this histologic finding in children do not differ significantly from those found in adults, with CD, IBD, Helicobacter pylori (H. pylori), NSAID use, and autoimmune conditions being reported. However, approximately 40% of children have no apparent explanation for the increased IELs.

Non-steroidal anti-inflammatory drugs. NSAID use has been shown to cause duodenal histopathology nearly identical to what is found in early CD. The histopathology will typically resolve with drug discontinuation, but can recur with re-introduction of the drug. Possible etiologies for these findings are may be due to the direct toxic effects of NSAIDs or their metabolites, which are excreted in bile, or due to a hypersensitivity reaction. The most susceptible region to the effects of NSAIDs is the duodenal bulb and the presence of a neutrophilic infiltration in the lamina propria may be a potential clue to NSAID use. However, these histologic findings are non-specific, and may also be seen in those with H. pylori infection, which may also lead to chronic active gastritis on gastric biopsies.

In a large retrospective study, nearly 14% of patients with isolated IELs in the duodenum reported NSAID use, a percentage that may be inaccurately low due to under-reporting by patients. Other studies reported NSAID use in over 20% of those with duodenal IELs. In addition, a number of those with documented CD, SIBO, H. pylori, IBD, and microscopic colitis were concurrently using NSAIDs, making it challenging to know the etiology of the histologic finding given the overlap in risk factors or exposures.

Inflammatory bowel disease. IBD has also been associated with lymphocytic duodenitis. Histologic clues to IBD in those with lymphocytic duodenitis can include endoscopic erosions, neutrophilic infiltration, crypt abscesses, edema, and granulomas, which are rarely seen. A non-tip predominance of IELs has also been reported.

In a study that reviewed all duodenal biopsies over a 10-year period, IBD was present in 74 patients who had increased IELs.

Table 1 Modified Marsh-Oberhuber classification for diagnosis of celiac disease.

| Type | Intraepithelial lymphocytes | Crypts | Villous blunting |
|------|-----------------------------|--------|----------------|
| 0    | Normal                      | Normal | None           |
| 1    | Increased                   | Normal | None           |
| 2    | Increased                   | Hyperplastic | None       |
| 3a   | Increased                   | Hyperplastic | Mild       |
| 3b   | Increased                   | Hyperplastic | Moderate   |
| 3c   | Increased                   | Hyperplastic | Severe (flat) |
| 4    | Increased                   | Atrophic | Severe (flat) |
and normal architecture, making up 7.2% of patients with this histologic finding. Among these patients, 13 had ulcerative colitis (UC), 54 had Crohn’s disease, and 3 had indeterminate-type IBD. The mean age of adult patients with UC and Crohn’s disease at the time of this histologic finding was 40 and 39 years, respectively, while mean duodenal IEL count for in UC and Crohn’s disease was 45 and 44 IELs per 100 epithelial cells, respectively.

LATE HISTOLOGIC MIMICKERS

Late histologic mimickers are characterized by having increased intraepithelial lymphocytes with no villous atrophy, and crypts that are either normal or have minimal hyperplasia. Late histologic mimickers are characterized by increased intraepithelial lymphocytes, partial or total villous atrophy, crypt hyperplasia, and chronic inflammation in the lamina propria.

Table 2 Early and late histologic mimickers of celiac disease

| Early histologic mimickers | Late histologic mimickers |
|----------------------------|---------------------------|
| Non-steroidal anti-inflammatory drugs | Medications (olmesartan, ipilimumab, colchicine, mycophenolate mofetil, methotrexate, and azathioprine) |
| Inflammatory bowel disease | Common variable immunodeficiency |
| Helicobacter pylori | Giardia |
| Small intestine bacterial overgrowth | Small intestine bacterial overgrowth |
| Self-limited gastroenteritis | Crohn’s disease |
| Autoimmune conditions | Autoimmune enteropathy |
| Unclassified | Collagenous sprue |
| Unexplained | Tropical sprue |
| | Whipple’s disease |
| | Enteropathy-associated T-cell lymphoma |
| | CD4+ T-cell lymphoma |
| | Unclassified sprue |

Early histologic mimickers are characterized by increased intraepithelial lymphocytes with no villous atrophy, and crypts that are either normal or have minimal hyperplasia. Late histologic mimickers are characterized by increased intraepithelial lymphocytes, partial or total villous atrophy, crypt hyperplasia, and chronic inflammation in the lamina propria.

In one study, adults with villous atrophy in the duodenum and negative CD serologies were recorded over a 10-year period. A total of 72 patients were identified who subsequently underwent a comprehensive testing, including HLA haplotyping, anti-enterocyte antibodies, Giardia stool antigen, human immunodeficiency virus testing, immunoglobulin levels, breath testing for SIBO, T-cell gene rearrangement studies, and detailed travel and medication review. Etiologies for the enteropathy were as follows: seronegative CD in 28%; medication-related villous atrophy in 26%; "unclassified sprue" in 14%; common variable immunodeficiency (CVID) in 16%; autoimmune enteropathy, giardiasis, tropical sprue, CD4+ small intestinal T-cell lymphoma, and SIBO each in 4%; collagenous sprue in 3%; and enteropathy-associated T-cell lymphoma, Crohn’s disease, and extensive gastric metaplasia each in 1%. Seronegative CD was defined as...
patients with negative TTG, deamidated gliadin peptide, and antiendomysial antibodies, positive HLA-DQ2 or DQ8, histology consistent with CD, clinical and/or histologic response to a gluten-free diet, and negative testing for other entities.34 Among 19 patients with medication-related villous atrophy, 16 were later linked to olmesartan, two to mycophenolate mofetil, and one to methotrexate.34

**Olmesartan.** Olmesartan medoxomil is the prodrug of olmesartan, an angiotensin II receptor blocker, used to treat hypertension. This drug was approved in the United States in 2002 and in Europe in 2003. Twenty-two patients referred to a tertiary care center for chronic diarrhea and/or weight loss who were found to have a serologically negative enteropathy were noted to be taking olmesartan.35 Intestinal biopsies showed villous atrophy in all 22 patients, while 15 of the 22 additionally had acute neutrophilic inflammation and 7 had the presence of excess collagen deposition.36 Discontinuation of olmesartan led to clinical response in all patients, with an average weight gain of 12.2 kg after drug withdrawal, and histologic recovery in all patients that underwent follow-up biopsies.35 Consequently, the US Food and Drug Administration released a warning in July 2013 that olmesartan can cause a sprue-like enteropathy.36 Subsequently, two separate studies, one in French and one in Spanish populations, demonstrated olmesartan-associated enteropathy in 36 and 11 patients, respectively.37,38 Among these three studies, some interesting observations were noted. The mean age for patients with olmesartan-induced enteropathy ranged from 70–72 years. The patients were on a mean dose of 40 mg daily and had been taking the drug for a mean of 2.3–3.1 years before the diagnosis was made.35,37,38 Diarrhea was universal in all patients while abdominal pain was present in 45–75%, and profound weight loss was noted in many. Positivity for HLA-DQ2 or DQ8 was noted in 61–100% of those tested, a percentage much higher than found in the general population.35,37,38 In the previously described study with 16 cases of olmesartan-induced enteropathy, 11 had prominent collagen deposition.34 Therefore, older age at onset, prominent collagen deposition, and neutrophilic inflammation in a patient with a serologically negative enteropathy should always prompt a careful medication review, even if the drug was started years previously; the presence of permissive HLA haplotyping may confer increased risk in those patients taking olmesartan.34

**Other medications.** Ipilimumab is a humanized monoclonal antibody against cytotoxic T-lymphocyte antigen 4 used to treat metastatic melanoma and advanced prostate cancer that has been associated with features of CD, autoimmune enteropathy, and IBD.39,40 Colchicine is a microtubule polymerization inhibitor that causes mitotic arrest. At low doses, colchicine is associated with minimal mucosal changes; however, at high doses, it can cause severe villous flattening, leading to a clinical enteropathy.41 Mycophenolate mofetil, an immunsuppressive agent used commonly in transplant patients, is associated with crypt and villi architectural changes and marked lamina propria inflammation that can mimic CD.42 Additionally, it can result in epithelial cell apoptosis similar to that noted in graft-versus-host disease.42 These patients can be difficult to manage, especially if alternative immunosuppressive agents are contraindicated or suboptimal. Methotrexate is an antimetabolite, antineoplastic agent that inhibits DNA and RNA synthesis and prevents crypt mitotic activity and leads to villous diminution.43 Finally, azathioprine is an immune modulator commonly used for autoimmune hepatitis and IBD, that has been reported to cause a small bowel enteropathy, which is reversible with drug discontinuation.44

**Collagenous sprue.** Collagenous sprue (CS), first described in 1970, results in malabsorption and diarrhea.45 While CS shares most of the histologic features found with CD, it also characteristically demonstrates an irregularly thickened layer of type I collagen adjacent to the surface epithelium.45,46 Normal collagen band thickness in the duodenum should be five microns or less; in CS, the collagen

---

*Figure 3 (a and b) Histologic features associated with late mimickers of celiac disease. Histologic features associated with late mimickers of celiac disease (in this case, drug-induced from olmesartan). Late histologic mimickers are characterized by increased intraepithelial lymphocytosis, partial or total villous atrophy, crypt hyperplasia, and chronic inflammation in the lamina propria. This figure also demonstrates a prominent collagen band that can be seen in cases of drug-induced enteropathy (a at 100 x, b at 200 x; Haemotoxylin and Eosin stain).*
band is thick, irregular, often wraps around capillaries, and may result in surface epithelial detachment. The link between CS and gluten is not well-defined; management often begins with a gluten-free diet, although most patients do not fully respond. Patients with refractory CS may require treatment with corticosteroids or immunosuppressants, and histologic changes may persist following treatment. As noted previously, the finding of CS should prompt a careful medication review.

**Combined variable immunodeficiency.** CVID can both cause clinical and/or histologic features of a small bowel enteropathy. A diagnosis of CVID is made using the following criteria: (1) IgG is reduced at least two standard deviations below normal levels; (2) at least one other immunoglobulin level is reduced (IgA and/or IgM); (3) there is a poor response to vaccines; and (4) other immunodeficiency states have been excluded. CVID can occur at any age, although it is most common in children and young adults less than 30 years of age. Due to impaired antibody response, respiratory and gastrointestinal tract infections are common, although the absence of recurrent infections should not rule out the disease.

Histologic findings commonly seen with CVID include reduced or absent plasma cells, increased IELs, glandular apoptosis, villous blunting, and lymphoid aggregates. However, approximately 30% of CVID patients have a normal number of plasma cells on intestinal biopsies. These patients should have their management directed towards their CVID, given a gluten-free diet is unlikely to be helpful once CD has been ruled out, which can be challenging to do in a CVID patient with permissive celiac haplotyping, as serologies may be difficult to interpret if both IgA and IgG levels are low.

**Small intestinal bacterial overgrowth.** Several studies have been performed examining the impact of SIBO on small bowel histology, with results that make it challenging to interpret the true range of impact that SIBO has. In a study of 52 subjects without a known history of SIBO, duodenal aspirates and biopsies were performed and 26 (50%) subjects were found to have SIBO. Twenty of the 26 were noted to have colonic-type bacteria on cultures. A comparison of patients with and without SIBO found no difference in villous height, crypt depth, villous/crypt ratio, and lamina propria cell counts. There was a statistical difference in lamina propria IgA plasma cell counts as well as IEL counts in the setting of colonic-type bacteria, both higher among patients with SIBO, yet with values within normal limits. One study found a significant, inverse correlation between advancing age and IEL counts after adjusting for SIBO. Another compared histologic findings in patients with SIBO to controls. Decreased villous/crypt ratio (< 3:1) was statistically more common in patients with SIBO (24%) compared to controls (7%). However, there were no significant differences between patients with SIBO and controls regarding IELs, crypt apoptosis, basal plasmacytosis, cryptitis/villitis, peptic duodenitis, erosions/ulcers, eosinophilia, and absence of goblet or Paneth cells. The degree of association between serologically negative enteropathy and SIBO needs to be further defined.

**Tropical sprue.** Tropical sprue (TS) is condition endemic to certain parts of the world, notably South Asia, Caribbean, Central, and South America. Symptoms include diarrhea and weight loss. Although there are no laboratory tests to diagnose TS, work-up classically reveals negative CD serologies, deficiencies in folate and vitamin B12, and low serum protein. Small bowel histology looks identical to that seen in CD, and imparts the importance of travel history in diagnosing this condition. Management of TS includes folate and B12 replacement along with antibiotics, such as a tetracycline derivative. Complete recovery is typically expected in travelers who develop TS; however, in endemic sprue, up to 50% of the population may have clinical relapse.

**Autoimmune enteropathy.** Autoimmune enteropathy is a rare cause of intractable diarrhea characterized by auto-antibodies in the serum and small bowel enteropathy.
While the condition commonly affects infants, it is being increasingly recognized in adults. A diagnosis of autoimmune enteropathy is made using the following criteria: (1) chronic diarrhea (>6 weeks); (2) features of malabsorption; (3) representative small bowel histology (partial/total villous blunting, deep crypt lymphocytosis, increased crypt apoptotic bodies, and minimal intraepithelial lymphocytosis); (4) exclusion of other causes of villous atrophy; and (5) the presence of anti-enterocyte or anti-goblet cell antibodies. While these autoantibodies may be found in ~85% of those with autoimmune enteropathy, they tend to be non-specific. Contrary to other celiac mimickers, histology for autoimmune enteropathy typically reveals absence of goblet and Paneth cells, less prominent surface IELs, and a lymphoplasmacytic infiltrate. Many of these patients have refractory diarrhea and nutritional deficiencies, requiring immunosuppressive treatment. A particularly severe form of autoimmune enteropathy is known as the immunodysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX) syndrome, which results from mutations in the FOXP3 gene that controls regulatory T-cells.

**Whipple’s disease.** While Whipple’s disease is often listed among the disorders that can mimic CD both clinically and histologically, there are some notable differences. Whipple’s disease occurs predominantly in men with presentation often at 30–50 years of age. Patients present with multi-system complaints of diarrhea, weight loss, arthralgias, fever, lymphadenopathy, cardiac abnormalities, and neurologic features. While the duodenal villi are often described as blunted in patients with Whipple’s disease, they are typically broad, with the lamina propria expanded with macrophages; dilated lacteals and lipid deposition may also be noted. Periodic acid-Schiff staining of the small bowel tissue is typically positive in cases of Whipple’s disease, although this is non-specific and can also be seen in those with *Mycobacterium avium* intracellulare. As a result, polymerase chain reaction testing can be used for confirmation.

### Table 3

| Celiac disease (CD) mimicker | Histology | Diagnostic clues |
|-----------------------------|-----------|------------------|
| Autoimmune enteropathy      | Loss of goblet and Paneth cells, more neutrophils, decreased villous:crypt ratio | Can check anti-enterocyte and anti-goblet cell antibodies |
| Bacterial overgrowth        | May not have any change other than mildly | Look for other causes of enteropathy |
| Collagenous sprue           | CD-like with thickened collagen band (>5 microns), detached surface | Review medication list |
| Common variable immunodeficiency | Loss of plasma cells; lamina propria appears somewhat empty | Up to 30% with normal plasma cells; check immunoglobulin levels |
| *Helicobacter pylori* infection | May have increased IELs, but also neutrophils, gastric metaplasia | May have chronic active gastritis as a clue |
| Inflammatory bowel disease  | May have increased IELs as a sole duodenal feature | IELs more on sides or evenly distributed (non-tip predominant) |
| Medication effect           | May range from IELs only to total villous atrophy, +/– collagen | NSAIDs, omesartan, mycophenolate |
| Tropical sprue              | Identical to CD | Low B12 and folate |
| Whipple’s disease           | Broad rather than flat villi, filled macrophages, lipid deposits | Notable travel PAS staining and PCR testing |

IELs, intraepithelial lymphocytes; NSAIDs, non-steroidal anti-inflammatory drugs; PAS, periodic acid-Schiff.

### CONCLUSION

An algorithm for the work-up (Figure 4) and management (Figure 5) of patients with a serologically negative enteropathy can be used to guide clinicians. The evaluation of a patient with a serologically negative enteropathy necessitates a detailed evaluation by an expert gastrointestinal pathologist to ensure that adequate tissue has been obtained, and to be sure histologic clues favoring another diagnosis have not been overlooked. The histologic finding of duodenal IELs with normal villous architecture is being seen with increased frequency; while up to one-third of such cases have no known cause identified, NSAID use is a strong contributing factor. Several prescription medications can mimic CD and should be considered in all patients with a serologically negative enteropathy. Many mimickers of CD have clues to the underlying diagnosis (Table 3), and many have a targeted therapy. It is necessary to provide patients with a correct diagnosis and appropriate therapy rather than subject them to a lifetime of an unnecessary gluten-free diet.
6. Rampertab SD, Poonan N, Brar P et al. Trends in the presentation of celiac disease. Am J Med 2006; 113:355: e9–355.a14.
7. Green PHR, Fleischauer AT, Bhagat G et al. Risk of malignancy in patients with celiac disease. Am J Med 2003; 115: 191–195.
8. Cellier C, Delabesse E, Helmer C et al. Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. French Coeliac Disease Study Group. Lancet 2000; 356: 203–208.
9. Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease. Gut 2010; 59: 547–557.
10. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome.
11. Riedl A, Schmidtmann M, Stengel A et al.
12. Lovell RM, Ford AC. Prevalence of gastro-esophageal reflux-type symptoms in individuals with irritable bowel syndrome in the community: a meta-analysis. Am J Gastroenterol 2012; 107: 1001–1007.
13. Ford AC, Manwaha A, Lim A et al. Systematic review and meta-analysis of the prevalence of irritable bowel syndrome in individuals with dyspepsia. Clin Gastroenterol Hepatol 2010; 8: 401–409.
14. Ford G, Loundou A, Hamdani N et al. Anxiety and depression comorbidities in irritable bowel duodenum (IBD): a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci 2014; 264: 651–660.
15. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. Gastroenterology 2016; 150: 1522–1527.e2.
16. Longstreth GF, Thompson WG, Chey WD et al. Functional bowel disorders. Gastroenterology 2006; 130: 1480–1491.
17. Grace E, Shaw C, Whealen K et al. Review article: small intestinal bacterial overgrowth prevalence, clinical features, current and developing diagnostic tests, and treatment. Aliment Pharmacol Ther 2013; 38: 674–688.
18. Singh VV, Tookes PP. Small bowel bacterial overgrowth: presentation, diagnosis, and treatment. J Gastroenterol Hepatol 2008; 23: 356–372.
19. Khosrini R, Dai S-C, Lezcano S et al. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. Dig Dis Sci 2013; 58: 1443–1454.
20. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med 2006; 391: 2069–2078.
21. Bernstein CN. Treatment of IBD: where we are and where we are going. Curr Opin Gastroenterol 2015; 31: 110–119.
22. Oberhuber G, Granditsch G, Vogelsand H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol 1999; 11: 1185–1194.
23. Ferguson A, Murray D. Quantitation of intraepithelial lymphocytes in human jejunum. Gut 1977; 12: 986–994.
24. Veress B, Franzén L, Bodin L et al. Duodenal intraepithelial lymphocyte-count revisited. Scand J Gastroenterol 2004; 39: 138–144.
25. Hayat M, Cairns A, Dixon MF et al. Quantitation of intraepithelial lymphocytes in human jejunum: what is normal? J Clin Pathol 2002; 55: 393–394.
26. Kakar S, Nehra V, Murray JA et al. Significance of intraepithelial lymphocytosis in small bowel biopsy samples with normal mucosal architecture. Am J Gastroenterol 2003; 98: 2027–2033.
27. Mahadeva S, Wyatt J, Howdle PD. Is a raised intraepithelial lymphocyte count with normal villous architecture clinic relevant? J Clin Pathol 2002; 55: 424–428.
28. Shmidt E, Smyrk TC, Boswell CL et al. Increasing duodenal intraepithelial lymphocytosis found at upper endoscopy: time trends and associations. Gastrointest Endosc 2014; 80: 105–111.
29. Ariz I, Evans KE, Hopper AD et al. A prospective study into the aetiology of lymphocytic duodenitis. Aliment Pharmacol Ther 2010; 32: 1392–1397.
30. Shmidt E, Smyrk TC, Faubion WA et al. Duodenal intraepithelial lymphocytosis with normal villous architecture in pediatric patients. J Pediatr Gastroenterol Nutr 2013; 56: 51–55.
31. Freeman HJ. Sulin-dac-associated small bowel lesion. J Clin Gastroenterol 1986; 8: 569–571.
32. James Freeman H. Drug-induced sprue-like intestinal disease. Int J Celiac Dis 2016; 2: 49–53.
33. Patterson ER, Shmidt E, Oventenko AS et al. Normal villous architecture with increased intraepithelial lymphocytes a duodenal manifestation of Crohn disease. J Clin Pathol Am J Clin Pathol March 2015; 143:143: 445–450.
34. Green PHR, Degastaran M, Tennyson CA et al. Villous atrophy and negative celiac serology: a diagnostic and therapeutic dilemma. Am J Gastroenterol 2013; 108: 647–65345.