Celiac Disease and Other Causes of Duodenitis

Daniel R. Owen, BSc, MD; David A. Owen, MB, BCh, FRCPc

• Context.—Patients who receive an upper gastrointestinal endoscopic examination frequently have biopsies taken from the duodenum. Accurate interpretation of duodenal biopsies is essential for patient care. Celiac disease is a common clinical concern, but pathologists need to be aware of other conditions of the duodenum that mimic celiac disease.

Objective.—To review the normal histologic features of duodenal mucosa and describe the clinical and histologic findings in celiac disease and its mimics, listing the differentiating features of biopsies with villous atrophy and epithelial lymphocytosis.

Celiac disease (gluten-sensitive enteropathy) is relatively common in Western countries. However, several causes of duodenal inflammation other than celiac disease have been described and require diagnostic consideration. Causes of duodenal inflammation other than celiac disease may demonstrate the characteristic histologic features of celiac disease, including distortion of villous architecture, prominent infiltration of the lamina propria by inflammatory cells, and increased numbers of intraepithelial lymphocytes (IELs). Here we review the most up-to-date clinical and pathologic criteria for the diagnosis of celiac disease as well as the most common causes of duodenal inflammation that can mimic celiac disease (Table).

NORMAL APPEARANCES

In the investigation of suspected malabsorption, biopsies may be obtained from both the first part of the duodenum (the duodenal bulb) and the second part of the duodenum. Interpretation of the duodenal biopsies must allow for differences between the first and second parts of the duodenum and for the presence of lymphoid aggregates. Both parts of the duodenum have a villous length to crypt depth ratio that is approximately 3:1 to 5:1 (Figure 1). However, in the duodenal bulb, the number of inflammatory cells in the lamina propria is greater, and the villi tend to be shorter and broader, often with branching. These differences in normal histology reflect greater acidity in the lumen of the duodenal bulb.1,2 Lymphoid aggregates are a normal finding in the duodenum, and the overlying villi may be distorted or abnormally short. Duodenal IELs are scattered between absorptive cells and goblet cells. Both the first and second parts of the duodenum typically contain fewer than 25 to 30 IELs per 100 epithelial cells. The IELs are predominantly T lymphocytes that coexpress CD3 and CD8 antigens, although occasional T lymphocytes lack expression of CD8 antigen.3

ADEQUACY OF BIOPSIES

It has recently been appreciated that celiac disease may be patchy and that biopsy changes may be confined to the duodenal bulb.4–6 For this reason, biopsies obtained from both the first part (1 or 2 biopsies taken at the 12 o’clock or the 6 o’clock position or both) and second part (at least 4 biopsies) of the duodenum are recommended.7 Well-oriented biopsies are preferred, with at least 3 adjacent villi present for evaluation. If adequate sampling is not obtained, subtle diagnostic changes may be missed.

CELIAC DISEASE

In North America and Europe, celiac disease is the most common cause of chronic malabsorption and appears to be underdiagnosed.7 In the United States, the prevalence of celiac disease has been estimated at 0.71%.8 However, a recent study has shown a higher prevalence of undiagnosed celiac disease (1.1%) in individuals ages 18 to 50 years.9 Many individuals with celiac disease are asymptomatic (latent celiac disease) or minimally symptomatic (occult celiac disease), whereas others may present with a wide variety of symptoms, including diarrhea, steatorrhea, weight loss, bloating, flatulence, abdominal pain, iron-deficiency anemia, bone disease, and skin disease.7 Dermatitis

Data Sources.—The study comprises a literature review of pertinent publications as of November 30, 2016.

Conclusions.—Celiac disease is a common cause of abnormal duodenal histology. However, many of the histologic features found in the duodenal biopsy of patients with celiac disease are also present in other conditions that affect the small bowel. Diagnostic precision may be enhanced by obtaining a careful patient history and by ancillary laboratory testing, particularly for the presence of antitissue transglutaminase antibodies. (Arch Pathol Lab Med. 2018;142:35–43; doi: 10.5858/arpa.2016-0608-RA)
herpetiformis is regarded as a cutaneous manifestation of celiac disease, as 75% to 90% of patients with this skin condition have either symptomatic or latent celiac disease. Almost all patients with dermatitis herpetiformis will have positive serologic testing for anti–tissue transglutaminase (anti-tTG) antibodies. Latent celiac disease is also present in approximately 10% of the first-degree relatives of individuals receiving a diagnosis of celiac disease. Presently, it is not known whether the symptoms of celiac disease correlate with the severity of the histologic manifestations or the length of the small bowel involved.

Celiac disease involves gluten-induced injury to the small intestine, with loss of surface area available for nutrient absorption. Gluten is found in wheat, barley, and rye, and their byproducts, but not in rice or potatoes. The injury occurs following an inappropriate cell- and antibody-mediated immunologic reaction to gliadin, a peptide generated from digestion of dietary gluten by duodenal brush border enzymes. Exposure of the duodenal enterocytes to gliadin stimulates cytotoxic intraepithelial T-lymphocyte-mediated damage of the duodenal epithelium. Once absorbed, gliadin becomes deamidated by tTG, an enzyme present in the duodenal lamina propria. Binding of deamidated gluten to human leukocyte antigen (HLA) on antigen-presenting cells in the duodenal lamina propria triggers a gliadin-specific, CD4+ T-lymphocyte-mediated immune response.

Genetic predisposition is an important determinant of the epidemiology of celiac disease because almost all individuals with the disease harbor the HLA DQ-2 or DQ-8 genotype. Serologic testing for gluten sensitivity is widely available but has not replaced duodenal biopsy as a sole diagnostic modality. The most commonly employed serologic test for gluten sensitivity is the anti-tTG antibody test, which has a sensitivity and specificity of approximately 95%. However, the sensitivity and specificity of the anti-tTG test vary between laboratories. In equivocal cases, testing for the presence of anti-endomysial antibodies may be helpful, whereas testing for anti-gliadin antibodies is no longer recommended. The anti-tTG antibody test is based on detecting the presence of immunoglobulin (Ig) A antibodies. The test may yield a false-negative result in patients with IgA deficiency. However, anti-tTG testing based on detection of IgG antibodies can be used in IgA-deficient patients. Generally, a higher titer of anti-tTG antibodies indicates a higher probability of a true-positive test result. A falling anti-tTG antibody titer parallels the elimination of gluten from the diet and largely obviates the need for additional duodenal biopsies to confirm treatment response.

Proposed diagnostic algorithms allow for the diagnosis of celiac disease without duodenal biopsy in some cases. For example, Catassi and Fasano have proposed that 4 of 5 criteria are required for a diagnosis of celiac disease (the “4 out of 5 rule”). According to the rule, celiac disease can be diagnosed in an individual with 4 of the following features: typical symptoms of the disease, serum IgA anti-tTG antibodies at a high titer, HLA DQ-2 or DQ-8 genotype, a positive duodenal biopsy, and clinical response to a gluten-free diet. Thus, if the rule is applied, histologic evidence of celiac disease in duodenal biopsies need not necessarily be obtained for the diagnosis of celiac disease. The most recent guidelines on the diagnosis of celiac disease from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition likewise allow for the diagnosis of celiac disease without duodenal biopsies in symptomatic children where the anti-tTG antibody titer exceeds 10 times the upper limit of the normal range, anti-endomysial antibodies are detected in a separate blood sample, and HLA testing shows the DQ-2 or DQ-8 genotype. Nevertheless, recognizing variation in the diagnostic accuracy of clinical findings and serologic testing, the American College of Gastroenterology (ACG) and the British Society of Gastroenterology (BSG) both regard biopsy of the duodenum as an essential component of the diagnosis of celiac disease. A pretreatment duodenal biopsy is also useful for evaluation of
a patient suspected of having celiac disease whose symptoms do not respond to a gluten-free diet.

The 3 major features of duodenal biopsies in patients with untreated celiac disease are intraepithelial lymphocytosis, increased numbers of inflammatory cells in the lamina propria, and villous atrophy. Formal counting of IELs is rarely required because intraepithelial lymphocytosis is usually obvious. In celiac disease there are typically more than 25 to 30 IELs per 100 epithelial cells (Figure 2). In instances where a formal count of intraepithelial lymphocytes is required, it is recommended to count the number of IELs per 100 epithelial cells across 5 villous tips.19

An increase in the number of lamina propria inflammatory cells is more challenging to assess. In untreated celiac disease, numbers of both lymphocytes and plasma cells are increased. Common variable immunodeficiency mimics many of the histologic features of celiac disease, including villous atrophy, lymphoid hyperplasia in the lamina propria, and increased numbers of IELs.20 However, the absence (or rarity) of plasma cells in the lamina propria of individuals with common variable immunodeficiency is an important clue in the differential diagnosis. In order to avoid misdiagnosing common variable immunodeficiency, the presence of plasma cells in the lamina propria of a duodenal biopsy should always be established before making the diagnosis of celiac disease. Patients suspected of having common variable immunodeficiency should also be investigated for other mimics of celiac disease, including giardiasis and small bowel bacterial overgrowth.

Neutrophils and eosinophils may be identified in addition to chronic inflammatory cells within the duodenal lamina propria of an individual with celiac disease. More pronounced neutrophilic inflammation, including cryptitis and crypt abscesses, can also be present. A study by Moran and colleagues21 showed prominent duodenal neutrophilia in 56% of pediatric patients and 28% of adult patients with celiac disease. Eosinophilic inflammation is usually less prominent in celiac disease, but eosinophils in the duodenal lamina propria may vary between 3 and 50 per high-power field.22

Villous atrophy is best assessed by the system devised by Marsh23 and modified by Oberhuber.24 The type 1 lesion consists of increased numbers of IELs with a normal villous architecture. A type 1 lesion may be seen in patients with latent and occult celiac disease but is relatively nonspecific and may also be encountered in duodenal inflammatory bowel disease, viral infections, and other conditions. The type 2 lesion consists of increased numbers of IELs and crypt hyperplasia, with a villous height to crypt depth ratio reduced to less than 3:1. The type 3 lesion is divided into three grades: 3a, which is intraepithelial lymphocytosis plus partial villous atrophy (Figure 3); 3b, which is intraepithelial lymphocytosis plus subtotal villous atrophy (Figure 4); and 3c, which is total villous atrophy, where the mucosal profile resembles large bowel mucosa. In the type 4 lesion, the mucosa is atrophic with or without IELs.

The response to a gluten-free diet can be assessed by serial measurement of anti-tTG antibodies, without the need for follow-up biopsies in most cases.7 Nevertheless, some patients who strictly adhere to a gluten-free diet can achieve complete recovery of normal duodenal histology. A study by Rubio-Tapia and colleagues25 identified that in practice, 66% of individuals with celiac disease who receive follow-up biopsies show complete mucosal recovery at 5 years after diagnosis. Although not all individuals included in the study adhered strictly to a gluten-free diet, the median time to complete mucosal recovery was approximately 3.8 years.

Nonceliac gluten sensitivity (NCGS) is a recently recognized condition distinct from celiac disease.26 Patients

---

**Figure 2.** Celiac disease with epithelial lymphocytosis. There are well in excess of 25 lymphocytes per 100 epithelial cells. The lymphocytes are almost exclusively T cells (immunohistochemical stain for CD3, original magnification \( \times 200 \)).

**Figure 3.** Celiac disease Marsh Oberhuber type 3a (partial villous atrophy). Villous stunting is present, resulting in a villous height to crypt depth ratio of approximately 1:1 (hematoxylin-eosin, original magnification \( \times 40 \)).

**Figure 4.** Celiac disease Marsh Oberhuber type 3b (subtotal villous atrophy). Villi are still present, but they are broad and stubby (hematoxylin-eosin, original magnification \( \times 40 \)).
typically present with symptoms that mimic irritable bowel syndrome, such as abdominal pain and diarrhea. The duodenal biopsy and anti-tTG antibody levels are within normal limits in NCGS. Despite initial skepticism regarding NCGS, recent evidence from controlled trials shows that some patients benefit from a gluten-free diet. Furthermore, some individuals with NCGS have comorbid allergic, autoimmune, or psychiatric disorders, the symptoms of which appear to be reduced in some cases by the elimination of dietary gluten. The pathologic mechanism of gluten sensitivity in NCGS is currently unknown and requires further study.

REFRACTORY SPRUE

Refractory sprue (RS) is a rare condition representing an absent or incomplete response to a strict gluten-free diet after 6 to 12 months in an individual who has serologic or genetic evidence of celiac disease. Malabsorption, intraepithelial lymphocytosis, and villous blunting persist or recur in patients with RS despite strict adherence to a gluten-free diet. Individuals with RS typically show serologic evidence of gluten sensitivity at the time of their initial diagnosis of celiac disease, and almost all have either the HLA-DQ-2 or DQ-8 genotype. At the time of the diagnosis of RS, up to 30% of patients show persistent serologic evidence of gluten sensitivity despite strict adherence to a gluten-free diet. The term RS should not be used in patients without prior evidence of gluten sensitivity. The diagnosis of unclassified sprue is preferred in patients with a sprue-like initial clinical presentation without evidence of gluten sensitivity. Refractory sprue may be divided into 2 types on the basis of IEL phenotype and genetics. Type 1 RS is characterized by a normal IEL immunophenotype with positivity for CD3 and CD8 antigens. The IELs in type 2 RS show an abnormal immunophenotype with surface negativity for CD3, CD4, and CD8 antigens, as well as preserved cytoplasmic expression of CD3 (CD3δ) antigen in greater than 50% of the IELs. Monoclonal or oligoclonal rearrangement of the T-cell receptor γ gene may also be demonstrated by polymerase chain reaction in type 2 RS. Patients with type 1 RS (with normal IEL immunophenotype and no clonal T-cell receptor gene rearrangement) usually respond to standard immunosuppressive therapy. Patients with type 2 RS have a risk of progression to enteropathy-associated T-cell lymphoma. Type 2 RS is typically refractory to standard immunosuppressive therapy and may require treatment with chemotherapeutic or immunomodulatory drugs.

The duodenal biopsy in RS may show severe flattening combined with mucosal thinning (a modified Marsh-Oberhuber type 4 lesion). In addition, the biopsies may demonstrate extensive basal plasmacytosis and subepithelial collagenous thickening (collagenous sprue). Collagenous sprue resembles both collagenous colitis and collagenous gastritis, with a patchy subepithelial collagen layer greater than 10 μm thick and showing entrapment of capillaries and fibroblasts. A trichrome stain can be helpful because the diagnostic features of collagenous sprue may be patchy. The term ulcerative jejunitis is now understood to be synonymous with lymphoma complicating celiac disease. Enteropathy-associated T-cell lymphoma is the most common form of lymphoma that complicates RS; however, B-cell lymphomas arising in the setting of RS have also been described. The first part of the duodenum can be regarded as an extension of the gastric antrum that is exposed to acidic gastric secretions. Peptic duodenitis results from an excess of gastric acid relative to bicarbonate in the proximal duodenum, most often as a result of gastric Helicobacter infection. Up to 44% of patients with Helicobacter gastritis also have proximal duodenitis with increased numbers of IELs. The mean number of duodenal IELs is significantly increased in those with Helicobacter gastritis compared with those with non-Helicobacter gastritis. Treatment of Helicobacter infection has also been shown to reduce duodenal IEL count.

The duodenal biopsy appearances of peptic duodenitis are usually those of a Marsh type 1 lesion (epithelial lymphocytosis with normal villi). Intraepithelial lymphocytes are present along the villi and in the crypts. The lamina propria is expanded and contains an excess of chronic inflammatory cells, including plasma cells, lymphocytes, and macrophages. Reactive hyperplasia of Brunner glands may also occur. Foci of gastric metaplasia in the duodenum (Figure 6) that may or may not harbor Helicobacter organisms are encountered in a small number of individuals with peptic duodenitis. Neutrophil infiltrates are present in the lamina propria in 8% of cases, but they usually do not involve the epithelial surface. However, in moderate to severe peptic duodenitis, the duodenal epithelium may show widespread infiltration by neutrophils, and reactive changes, such as a syncytial growth pattern, mucin depletion, nuclear hyperchromasia, and increased mitotic activity. Duodenal mucosal erosion and ulceration develop in the most severe cases (Figure 6).

PEPTIC DUODENITIS

Patients with both ulcerative colitis and Crohn disease may develop duodenitis, although they uncommonly present with upper gastrointestinal symptoms. The biopsy appearances of ulcerative colitis in the duodenum resemble those in the large bowel, consisting of diffuse active chronic inflammation including cryptitis and crypt abscess formation. The lamina propria may show basal plasmacytosis, and the villi may be distorted. Ulceration is present in severe cases. The reported frequency of upper gastrointestinal inflammation in ulcerative colitis is low, varying from 3% to 10%. Duodenal involvement by ulcerative colitis appears to be more common in those with pancolitis compared with those with left-sided colitis.

Crohn disease involving the duodenum is much more common than duodenal ulcerative colitis and is present in 26% of Crohn patients. Duodenal Crohn disease typically also involves the stomach (focal active gastritis). The histologic appearance of Crohn disease in the duodenum is similar to that in the terminal ileum and involves patchy active inflammation with neutrophils in the lamina propria and surface epithelium. Many cases of duodenal Crohn disease also show intraepithelial lymphocytosis (Figure 7). Deep mucosal inflammation and granulomata are present in 19% and 9% of cases, respectively. Aphthoid ulceration, structuring, and fistulation are uncommon. The diagnosis of duodenal Crohn disease may be relatively straightforward in cases that show granulomatous inflammation. Although duodenal granulomas are present only in a minority of cases, patients with duodenal Crohn disease should have...
more prominent involvement of the terminal ileum, the large bowel, or both.

**DRUG-INDUCED DUODENITIS**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common cause of duodenitis, and it has been estimated that duodenitis occurs in more than 60% of long-term NSAID users. The histologic manifestations of NSAID-associated duodenitis bear some resemblance to those of celiac disease, although NSAID-associated duodenitis does not produce many of the clinical symptoms typically associated with celiac disease. It should be noted, however, that both long-term NSAID use and celiac disease can produce iron-deficiency anemia.

Early NSAID-associated duodenitis is characterized by nonspecific infiltration of the lamina propria by neutrophils and plasma cells, accompanied in some cases by low-grade villous blunting and intraepithelial lymphocytosis. In advanced disease, mucosal erosions (often multiple) and even deep ulcers resulting in hemorrhage and perforation may develop (Figure 8). Peptic duodenitis is the main differential diagnosis of NSAID-associated duodenitis. Differentiation between the 2 entities is made simpler if both gastric and duodenal biopsies are obtained. Foci of gastric metaplasia in the duodenum are an important diagnostic clue because they do not occur in NSAID-associated duodenitis.

Olmesartan is an angiotensin II receptor blocker that is used to treat hypertension. Its use induces severe diarrhea in some individuals. Olmesartan-induced diarrhea is associated with duodenal inflammation, in many cases indistinguishable from that seen in celiac disease (Figure 9). Of patients with symptomatic olmesartan-induced diarrhea, 92% have partial or complete villous atrophy, and 61% have increased IELs ranging from 25 to 100 per 100 epithelial cells. However, the duodenitis of celiac disease may have some differences from olmesartan-induced duodenitis (olmesartan enteropathy). Olmesartan enteropathy may show abundant infiltration of the lamina propria by neutrophils and lymphocytes with foci of crypt cell apoptosis. Furthermore, 22% of cases of olmesartan enteropathy show deposition of subepithelial collagen resembling that seen in collagenous sprue.

Mycophenolate is an immunosuppressive drug commonly used to prevent acute allograft rejection. Gastrointestinal damage from mycophenolate usually manifests in the colon but may also be present in the duodenum. The histologic features are very similar to those of acute graft-versus-host disease (GVHD), making distinction of the 2 conditions difficult. Changes characteristic of mycophenolate-induced duodenitis include crypt architectural disarray, edematous lamina propria with chronic inflammation, and cystic dilatation of the duodenal crypts. The epithelial lining of the dilated crypts is often flattened and shows increased apoptosis as well as luminal neutrophils and apoptotic debris. The presence of eosinophils (greater than 15 per 10 high-power fields) is more in keeping with mycophenolate-induced damage, whereas the presence of endocrine cell aggregates and hypereosinophilic crypt degeneration suggests GVHD.

Gastrointestinal damage in acute GVHD typically occurs following bone marrow transplantation, but rarely can also occur subsequent to solid organ transplantation. Four grades of GVHD are customarily recognized: grade 1 shows occasional apoptotic cells without crypt damage; grade 2 shows apoptosis with loss of individual crypts; grade 3 shows apoptosis plus loss of 2 or more adjacent crypts with or without apoptotic crypt abscess formation (Figure 10); and grade 4 shows almost total loss of crypts, with ulceration and replacement of the mucosa by granulation tissue (denudation). The apoptosis is most intense where regenerating enterocytes are found at the bases of the crypts. Because the lamina propria does not contain excess chronic inflammatory cells in most instances of acute GVHD, grades 2 and 3 acute GVHD are more likely to be misdiagnosed as mycophenolate-induced mucosal damage.

**AUTOIMMUNE ENTEROPATHY**

Autoimmune enteropathy is a rare condition characterized by immune-mediated intestinal mucosal atrophy. It may occur in both children and adults, with some differences in histologic findings. Some cases occur as part of a recognized syndrome—for example, the syndrome of immunodysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX syndrome) caused by a mutation in the FOXP3 gene, and the autoimmune polyglandular syndrome, involving a diverse array of symptoms, such as autoimmune phenomena, polyendocrinopathy, candidiasis, and ectodermal dystrophy.

Autoimmune enteropathy usually affects the stomach, colon, and esophagus, as well as the small bowel. A study of 8 adults and 14 children ages 6 years or younger described 4 different histologic categories. A total of 52% of cases had chronic active duodenitis characterized by villous blunting, lamina propria expansion by mononuclear cells, neutrophilic cryptitis, and crypt abscess formation; 16% of cases showed inflammation with apoptosis and resembled acute GVHD; and 5% of cases were indistinguishable from celiac disease, with extensive intraepithelial lymphocytosis. All remaining cases had a mixed pattern. A study including only children showed similar results, except that the pattern of injury resembling acute GVHD was more common.

Many patients with autoimmune enteropathy have circulating antibodies to both intestinal goblet cells and enterocytes. Occasionally, patients in whom the biopsies show a complete loss of intestinal goblet cells have been described. However, the significance of these findings to the pathogenesis of autoimmune enteropathy and their usefulness in making the diagnosis remain unknown.

**TROPICAL SPRUE AND ENVIRONMENTAL ENTEROPATHY**

Tropical sprue affects residents of and visitors to tropical areas, such as Central America and Southeast Asia. Patients typically present with profuse diarrhea, weight loss, and malabsorption, commonly resulting in deficiencies of folate and vitamin B₁₂. Bacterial, viral, or parasitic infection is thought to be the cause of tropical sprue. Bacteria, including *Klebsiella*, *Enterobacter*, and *Escherichia* species, have been identified in patients with tropical sprue, although a specific causative pathogen has not yet been identified. Symptomatic improvement in response to a prolonged course of broad-spectrum antibiotic therapy has been observed in some patients. In a recent study by Brown and colleagues, the duodenal biopsy in 75% of cases of tropical sprue showed partial villous blunting (Marsh–Oberhuber type 3a); however, complete mucosal flattening was rarely observed. Intraepithelial lymphocytosis was typically present, with a

Arch Pathol Lab Med—Vol 142, January 2018

Celiac Disease and Duodenitis—Owen & Owen

39
Figure 5. Gastric metaplasia in peptic duodenitis. The mucosal surface is covered by gastric type epithelium with columnar cells containing neutral mucin. At the base of the mucosa small bowel epithelium persists with goblet cells containing acidic mucin (periodic acid–Schiff and diastase with Alcian blue at pH 2.5, original magnification ×100).

Figure 6. Peptic duodenitis with mucosal erosion. The exudate contains large numbers of neutrophils (hematoxylin-eosin, original magnification ×100).

Figure 7. Crohn duodenitis. Note focal crypt damage with epithelial lymphocytosis (hematoxylin-eosin, original magnification ×400).

Figure 8. Nonsteroidal anti-inflammatory drug-associated enteropathy. Erosion is present without a heavy neutrophil infiltrate. Presumably, acute inflammation is suppressed by the drug (hematoxylin-eosin, original magnification ×100).
mean IEL count of approximately 77 per 100 epithelial cells. The number of eosinophils in the lamina propria of patients with tropical sprue (mean of 26.5 per high-power field) was also greater than the number in patients with celiac disease (mean of 14.6 per high-power field). In contrast to celiac disease, the histopathologic changes in tropical sprue are usually much more prominent in the distal small bowel than in the duodenum, consistent with the hypothesis that tropical sprue has an infectious etiology. Patients with tropical sprue do not have elevation of anti-tTG antibodies.

Environmental enteropathy appears to be closely related to tropical sprue, and the histologic features of the duodenal biopsy are essentially the same in both diseases. Environmental enteropathy also does not involve elevation of anti-tTG antibodies. The disease is widespread throughout the developing world and is considered a leading cause of malnutrition in developing countries.51 Patients, typically small children, present with poor growth, weight loss, and malabsorption. They may or may not have diarrhea. Constant fecal-oral contamination with exposure to fecal pathogens, poor nutrition, and alteration of immune function are all likely contributing causes, although the etiology and pathogenesis remain incompletely defined. Unlike tropical sprue, environmental enteropathy does not respond to antibiotic therapy. Nutritional intervention can result in healing of mucosal damage in the short term; however, recovery of body mass and improvement in other indicators of overall nutrition typically take longer to occur. Long-term improvement is unlikely without continual follow-up and treatment.52

COW’S MILK AND SOY PROTEIN ALLERGY

Allergy to protein in soy and cow’s milk is distinct from the inability to digest lactose because of an insufficiency of lactase in the small bowel (lactose intolerance). Cow and soy milk protein allergy involves an antibody (often IgE) or T-cell–mediated hypersensitivity reaction.53 Allergy to cow’s milk or soy protein is encountered in children and infants who present with severe diarrhea (sometimes bloody), vomiting, weight loss, and abdominal pain. Laboratory findings include hypoalbuminemia and iron-deficiency anemia, with a negative anti-tTG antibody test result. Peripheral blood eosinophilia may be encountered in some patients with cow’s milk or soy protein allergy.

Duodenal histologic changes in patients with cow’s milk or soy protein allergy vary.54-56 In individuals with a T-cell–mediated hypersensitivity reaction, the duodenal biopsies show changes similar to those seen in celiac disease (low-grade villous blunting and intraepithelial lymphocytosis). However, advanced lesions (Marsh–Oberhuber type 3b or 3c) are rarely encountered. In those with elevated IgA, the predominant biopsy finding is heavy mucosal eosinophilia, often with sheets of eosinophils. Cases with abundant tissue eosinophilia may be described as eosinophilic duodenitis, and are usually not accompanied by epithelial lymphocytosis. Such patients may also have eosinophilic protocolitis. In general, prominent tissue eosinophilia is suggestive of a non–gluten-induced enteropathy.

BACTERIAL OVERGROWTH

Bacterial overgrowth in the duodenum may occur because of stasis of intestinal contents either in a blind loop or because of a motility disorder arising, for example, from systemic sclerosis or diabetic neuropathy. The pathogenesis involves proliferation within the small bowel lumen of anaerobic bacteria that are normally present in the colon. The typical symptoms include diarrhea and steatorrhea. In some cases, depletion of vitamin B12 by the overgrowth of bacteria produces vitamin B12 deficiency. Duodenal biopsies in patients with bacterial overgrowth can have entirely normal results, although an ultrastructural study of bacterial overgrowth demonstrated damage to microvilli on the surface of the absorptive cells.57 The histology of the duodenal biopsy in bacterial overgrowth more often shows mild to moderate villous blunting and crypt hyperplasia, increased chronic inflammation in the lamina propria, and intraepithelial lymphocytosis. The distribution of the histologic abnormalities may be patchy, with histologically normal areas intervening.58 It is often impossible to distinguish bacterial overgrowth syndrome from celiac disease by morphology alone.59 The definitive diagnosis of bacterial overgrowth can be made by culture of small intestine aspirates. The diagnosis requires bacterial growth, chiefly of coliform bacteria, in excess of 10³ organisms per milliliter of fluid.60 Anti-tTG antibodies are not elevated in bacterial overgrowth syndrome.

HISTORICAL PERSPECTIVE AND CONCLUSIONS

The importance of dietary gluten in the pathogenesis of celiac disease was initially recognized in the scientific literature in the 1950s.61 Since then, various methods of diagnosing celiac disease, all of which involve both clinical and pathologic findings, have been proposed.7,13,17,18,62,63 In the 1960s, a series of duodenal biopsies was deemed necessary to confirm the diagnosis of celiac disease: the first to demonstrate the characteristic flat mucosal lesion in a symptomatic patient consuming gluten; the second to show complete or nearly complete histologic normalization with dietary treatment; and the third to show recurrence following a gluten challenge.62 In the 1990s, the criteria for celiac disease were revised such that diagnosis required only a single set of duodenal biopsies showing the characteristic mucosal features. However, the latter criteria required that the patient be consuming gluten at the time of the biopsy and that full clinical improvement be observed following establishment of a gluten-free diet.63 Around the same time, milder histologic manifestations of celiac disease, including the infiltrative and preinfiltrative lesions that formed part of the Marsh and Oberhuber classifications, were also recognized.64

Modern criteria for the diagnosis of celiac disease have incorporated serologic testing for anti-tTG antibodies and HLA genotyping.7,17,18 Some authorities have suggested that adolescent patients with anti-tTG antibodies greater than 10 times the upper limit of normal, positive endomysial antibodies, and an HLA-DQ2 or HLA-DQ8 genotype do not need duodenal biopsies for confirmation of a diagnosis.

Figure 9. Olmesartan enteropathy. Severe villous atrophy and mucosal inflammation are present with an appearance closely mimicking celiac disease (hematoxylin-eosin, original magnification x40).

Figure 10. Duodenal graft-versus-host disease, grade 3: There is apoptosis, and there are regenerative changes with adjacent extensive crypt damage and atrophy (hematoxylin-eosin, original magnification x400).
of celiac disease. However, in order to avoid errors of overdiagnosis or underdiagnosis in adults, the ACG and the BSG both continue to require duodenal biopsies for the diagnostic confirmation of celiac disease. According to the diagnostic algorithm proposed by the ACG, all diagnoses of celiac disease require both measurement of serum anti-tTG antibodies and histologic manifestations of celiac disease proven by duodenal biopsy. The ACG algorithm includes HLA genotyping in cases where the results of antibody testing and duodenal histology yield contradictory results.

Other conditions that commonly involve biopsy evidence of villous atrophy and epithelial lymphocytosis include: RS, drug-induced enteropathy, tropical sprue, environmental enteropathy, intolerance to other dietary proteins (cow’s milk and soy), and bacterial overgrowth. Use of the anti-tTG antibody test has greatly simplified the distinction of celiac disease from these other entities. If the results of serologic testing for gluten sensitivity are not available to the pathologist evaluating a duodenal biopsy, this should be noted in the report, along with a statement that the histologic diagnosis of suspected celiac disease should be confirmed by serologic testing.

References


Prepare Submissions Now for the CAP18 Abstract Program

Abstract and case study submissions to the College of American Pathologists (CAP) 2018 Abstract Program will be accepted beginning at noon Monday, January 8 through 5 p.m. Central time Friday, March 9, 2018.

Accepted submissions will appear on the Archives of Pathology & Laboratory Medicine Web site as a Web-only supplement to the September 2018 issue. Awards will be presented to the winners of the Top 5 Junior Member Abstract Program.

The CAP18 meeting will be held October 20–24 in Chicago. Visit the CAP18 Web site (www.cap.org/cap18) and the Archives Web site (www.archivesofpathology.org) for additional abstract program information as it becomes available.