

Celiac disease for the endoscopist

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Celiac disease, an autoimmune enteropathy caused by gluten in food, is now understood to be a disorder with an extremely wide range of presenting manifestations of variable severity. It is the result of sensitivity to ingested gluten in genetically susceptible people with the subsequent immune reaction leading to small bowel inflammation. This gives the characteristic mucosal lesion of increased intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia in the proximal small bowel. The classic malabsorptive symptoms of diarrhea and weight loss are only one facet of the spectrum of manifestations of this relatively common disease.¹⁻³ Symptoms may be subtle and many patients have subclinical or silent disease.³ Available data suggest that celiac disease has a prevalence of approximately 1:250-300 in western countries including the United States.⁴⁻⁶

CLINICAL MANIFESTATIONS

Over 50% of patients with celiac disease have no GI symptoms, and for those who do have symptoms, dyspepsia or anorexia may be the only complaint.¹⁻³ Because symptoms are often nonspecific, the diagnosis can be missed. However, even the classic symptoms may not lead to the diagnosis. For example, Dickey and McConnell⁷ found that on initial referral, diarrhea led to a diagnosis in only 72% and anemia in only 41% of patients.

Lassitude, weakness, and anorexia are the most common presenting features. Less than one-half of patients now present with diarrhea.^{8,9} Diarrhea is often mild, it can be intermittent, or it may occur only in the early morning. Furthermore, constipation may be the only intestinal complaint.¹⁰ As

regards weight loss, a study of celiac patients at initial presentation found that 22% were underweight and 35% were overweight; two thirds of men with the disease were overweight.¹¹ Celiac disease may present with nonspecific upper abdominal symptoms such as abdominal pain, nausea, and dyspepsia. Almost 50% of patients report dyspepsia, 50% dysphagia, 30% vomiting, and 14% noncardiac chest pain.^{12,13} Abdominal pain occurs in up to one third of patients and may prompt an erroneous diagnosis of irritable bowel syndrome.¹⁴

Glossitis or angular stomatitis is present in up to 90% of untreated patients. Recurrent aphthous ulcers may be the presenting feature of the disorder; these usually respond well to gluten withdrawal.¹⁵ Dental enamel defects are common, with the incisors and molars usually affected.¹⁶ Hair loss occurs and improves with elimination of gluten from the diet.¹⁷

Disorders of calcium and vitamin D absorption are common in all age categories of patients with celiac disease. Osteomalacia develops in more than 50% and can give rise to bone pain that is exacerbated by weight bearing. Osteopenia and osteoporosis occur in 26% and are associated with an increased risk of bone fractures.¹⁸

Various neurologic syndromes have been described in patients with celiac disease, although these are present in less than 10% of cases. Ataxia is the most common, usually a late-onset gait ataxia with only mild upper limb signs.¹⁹ A coexistent peripheral neuropathy is common, the legs again more affected than the arms, with numbness and paraesthesias.²⁰ Spinocerebellar degeneration and a progressive cerebellar syndrome may occur because of vitamin E deficiency.²¹ A proximal muscle weakness may be the presenting feature.²² Epilepsy has been found in 3% to 5% of patients who have celiac disease.²³ In particular, the disease has been associated with epilepsy and cerebral calcification.⁷

Reduced fertility has been reported in both men and women with celiac disease.^{24,25} For pregnant women who have the disease, there is an increased frequency of miscarriage, stillbirth, perinatal deaths, and intrauterine growth retardation.^{26,27}

Elevation of aspartate transaminase and alanine transaminase is common in celiac disease and is thought to reflect increased intestinal permeability.²⁸

Iron deficiency anemia is a common indication for endoscopy. Celiac disease is increasingly recognized as a cause of iron deficiency anemia, which may be the only manifestation of the disease. In a series of 798 patients with subclinical celiac disease, iron deficiency anemia was the most common presenting manifestation, occurring in 39% overall.³ Malabsorption of inorganic iron is thought to be the major cause of iron

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deficiency.^{29,30} Loss of iron because of mucosal sloughing of enterocytes and occult GI bleeding may also be contributory.^{31,32} In from 5% to 14% of patients evaluated for iron deficiency anemia, celiac disease has been found to be the cause.³³⁻³⁸ Iron deficiency caused by celiac disease responds poorly to iron supplementation but resolves on elimination of gluten from the diet.³⁷ In one prospective series, iron deficiency anemia caused by celiac disease resolved in 14 of the 18 patients at 6 months and 17 of 18 at 1 year after institution of a gluten-free diet without iron supplementation.³⁷ Given that celiac disease as a cause of iron deficiency anemia is relatively common, and that anemia can be corrected and potential complications prevented with dietary restriction, small bowel biopsy specimens should be obtained in all patients undergoing evaluation for iron deficiency anemia when an explanation has not been found.

Macrocytic anemia caused by folate or, less commonly, vitamin B₁₂ deficiency may be present.³⁹ Celiac disease accounts for 30% of cases of folate deficiency.⁴⁰ Rarely, hemolytic anemia may be noted in association of celiac disease.⁴¹ Hyposplenism occurs in up to 80% of patients.⁴² Splenic function improves with a gluten-free diet.

Associated diseases

Celiac disease has been associated with a variety of other diseases. Of patients with celiac disease, up to 6% have an IgA deficiency,⁴³ 5% are diabetic (control improves with a gluten-free diet),⁴⁴ 5% have thyroid disease,⁴⁴ and 10% have dermatitis herpetiformis.⁴⁵ Celiac disease has also been reported in association with primary biliary cirrhosis and autoimmune hepatitis.⁴⁶

Resistant celiac disease

Patients with resistant celiac disease are those in whom the disease, although initially responsive, no longer responds to a gluten-free diet and those in whom the disease has never responded to the elimination of gluten. Before categorizing a patient as having resistant disease it is important to determine whether gluten is slipping into the diet, whether inadvertently or through poor compliance. Meticulous attention to dietary history and consultation with a qualified dietitian is vitally important in the assessment of potentially resistant disease. Patients with resistant celiac disease are a heterogeneous population: some will respond to additional treatment with corticosteroids and immunosuppressive agents, the clinical condition of some will continue to deteriorate despite all treatment, some will have as yet undiagnosed lymphoma or ulcerative jejunoileitis, and some have collagenous colitis.⁴⁷

DIAGNOSIS

Given that celiac disease is essentially a histopathologic diagnosis for which small bowel tissue is required,⁴⁸ endoscopy plays a critical role in the identification of patients with this treatable disorder. It is thus incumbent upon the endoscopist to be fully aware of all of the technical aspects essential to procurement of adequate tissue samples from the small intestine if the diagnosis of celiac disease, with its lifelong burden of adherence to a gluten-free diet, is to be made expeditiously.

Serologic tests

Advances in serologic testing for celiac disease are likely to increase the number of patients referred for endoscopy specifically for the purpose of obtaining small bowel biopsy specimens. Furthermore, in the present era of open access endoscopy, the endoscopist must recognize the well-characterized endoscopic features of celiac disease because these may be the only clues to its presence in patients without symptoms and those with subtle manifestations of otherwise unrecognized disease. The serologic tests now available are highly reliable for the diagnosis of celiac disease and a positive test constitutes an indication for endoscopy.⁴⁹ These include antigliadin, antiendomysium, and anti-tissue transglutaminase antibodies.

Antiendomysium IgA antibodies react with the connective tissue around smooth muscle fibers.⁵⁰ Antiendomysium IgA has been shown to have a sensitivity of 94% to 100% and specificity of 93% to 100% for the diagnosis of celiac disease.⁵¹⁻⁵³ Because the test for antiendomysium antibody is an immunofluorescence assay, it is operator dependent, and interpretation may vary significantly among commercial laboratories.⁵⁴ Additionally, celiac patients with selective IgA deficiency will not be detected by antiendomysium antibody testing.⁵⁵ A large, multicenter study reported that 3% of patients with celiac disease had selective IgA deficiency, with all of these IgA deficient patients testing negative for antiendomysium IgA.⁵⁵ Antigliadin IgA and IgG antibodies are less sensitive and specific than antiendomysium antibodies. However, testing for antigliadin IgG antibody may detect the disease in patients with IgA deficiency in whom the diagnosis would be missed based on testing for antiendomysium IgA antibodies alone.^{51-53,55} Tissue transglutaminase, an enzyme that catalyzes protein cross linking, has been identified as the substrate against which antiendomysium antibodies react.⁵⁶ A human recombinant anti-tissue transglutaminase ELISA was found to have a 98.5 sensitivity with a 95% specificity when the results of IgA and IgG testing were combined.⁵⁷

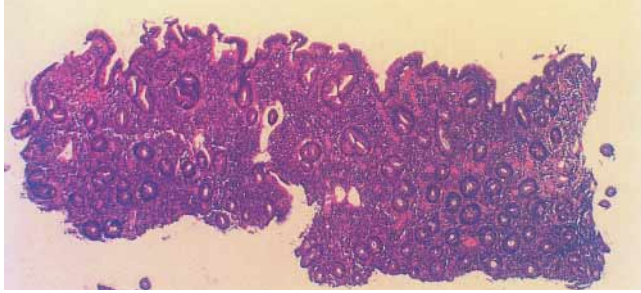


Figure 1. Photomicrograph of biopsy from jejunum obtained at push enteroscopy in a 74-year-old woman undergoing evaluation for iron deficiency anemia showing complete villous atrophy (H&E, orig. mag. $\times 100$). Courtesy of Dr. Joseph E. Willis.

Small bowel biopsy

Although serologic tests are highly sensitive and specific, the small bowel biopsy remains the standard for diagnosis of celiac disease. The essential requirements for the diagnosis include demonstration of hyperplastic villous atrophy of the small intestine and clinical remission of symptoms when gluten is removed from the diet (Figs. 1 and 2).⁴⁸ In the past, peroral suction devices/techniques were used to obtain tissue samples from the small bowel. Commonly used devices include the Watson capsule, the Crosby capsule, and the multipurpose tube, all of which have a similar mechanism.⁵⁸⁻⁶⁰ A capsule attached to an air-tight tube is guided under fluoroscopy to the region of the ligament of Treitz. When negative pressure is applied to the tube, mucosa is drawn into an open aperture at the side of the capsule. An internal cylindrical knife then guillotines the sample. With most devices, the specimen remains inside the capsule, which is then retrieved.

With the development of modern endoscopes and accessories circa 1970, duodenoscopy became a standard component of upper endoscopy, the latter becoming rightly known as EGD. In effect, this capability rendered the small bowel biopsy capsule obsolete for practical purposes. Moreover, the relative ease with which a small bowel biopsy specimen can be obtained at endoscopy may be contributing to an increase in the detection of celiac disease.⁶¹ There has been a long and lingering concern as to whether specimens obtained with an endoscopic forceps are satisfactory for the diagnosis of celiac disease. In particular, the ability to correctly orient an endoscopic biopsy specimen for sectioning has been questioned. The most recently published guideline from the European Society of Pediatric Gastroenterology and Nutrition in fact recommends the capsule biopsy, with orientation of the specimen under a dissecting microscope, as preferable to the endoscopic biopsy.⁴⁸ The suction capsule does provide larger



Figure 2. Photomicrograph of biopsy from distal duodenum in same patient as in Figure 1 at 6 months after institution of gluten-free diet showing partial villous regeneration (H&E, orig. mag. $\times 100$). Courtesy of Dr. Joseph E. Willis.

specimens that are more easily oriented for sectioning. However, studies comparing endoscopic with suction biopsies have failed to demonstrate the superiority of the suction capsule biopsy. A prospective study by Mee et al.⁶² compared duodenal and jejunal suction capsule biopsies to specimens obtained with a standard endoscopic forceps and a pediatric forceps from the second portion of the duodenum in 40 patients in whom malabsorption was suspected. Adequate tissue was obtained from the second part of the duodenum in 39 cases with the standard forceps and in 36 with the pediatric forceps. By comparison, an adequate specimen was obtained from the duodenum in only 28 cases and the jejunum in 32 cases with the capsule. In total, 14 patients were ultimately shown to have villous atrophy. This was correctly diagnosed in 13 patients based on evaluation of standard endoscopic forceps biopsies from the duodenum, compared with 12 patients based on examination of capsule biopsy specimens from the jejunum. Gillberg et al.⁶³ obtained endoscopic biopsy specimens from the second portion of the duodenum and Watson capsule specimens from the proximal jejunum in 48 patients with dermatitis herpetiformis. Villous atrophy was evident in endoscopic biopsies from 34 patients, whereas this diagnosis was made in only 31 patients based on assessment of capsule biopsy specimens. Achkar et al.⁶⁴ demonstrated that endoscopic and capsule biopsies were equivalent with respect to specimen adequacy, but only 12 minutes were required for procurement of endoscopic biopsy specimens versus 43 minutes for capsule biopsies, and moreover patients indicated a preference for the former. Granot et al.⁶⁵ retrospectively compared endoscopic biopsy specimens obtained in 30 children to

suction capsule biopsy specimens in the same number of children and found that both techniques yielded suitable samples.

There has been a concern that endoscopic forceps biopsy specimens are difficult to orient correctly for proper sectioning. If a specimen is not properly oriented before sectioning, normal villi cut tangentially may artifactually appear atrophic, thus leading to an incorrect diagnosis of celiac disease.⁶⁶ In all of the comparative trials cited above,⁶²⁻⁶⁵ endoscopic biopsy specimens were placed on filter paper with the mucosal side up to orient the specimens for subsequent sectioning. Occasionally, a dissecting microscope has been used to confirm proper orientation.⁶³

Biopsy specimens should always be obtained distal to the duodenal bulb because villi may be blunted or even absent over Brunner's glands, which are found predominantly in the duodenal bulb.⁶⁷ Specimens from the second portion of the duodenum provide information that is equivalent to that obtained with jejunal biopsies, and therefore a standard-length upper endoscope can be used.⁶⁸ The so-called "jumbo," endoscopic forceps provides larger specimens of excellent quality that are likely to contain adequate numbers of villi. However, one study comparing specimens obtained with a standard (8 mm) forceps to specimens procured with a jumbo (9 mm) forceps demonstrated that the former yields data comparable with that of the latter as long as 7 step sections were made from each sample.⁶⁹

Available data therefore indicate that endoscopic biopsies are equivalent, if not superior, to suction capsule biopsies. Additional advantages of the endoscopic approach include the ability to obtain multiple specimens and to inspect the upper GI tract. The latter can be particularly advantageous when symptoms and other findings do not strongly suggest celiac disease. Although endoscopy may require administration of sedative drugs, the need for fluoroscopy is eliminated and there is certitude as to the region of the small intestine from which the specimens were obtained. For these reasons, endoscopy is generally regarded as the method of choice for the diagnosis of celiac disease. A minimum of 4 specimens should be obtained from the second portion of the duodenum and immediately placed, mucosal side up, on filter paper. When the suspicion of celiac disease is high, an endoscope with a large accessory channel should be used so that specimens can be obtained with a jumbo forceps.

Endoscopic findings

It has long been known that celiac disease can produce changes in the appearance of small intestine on barium contrast radiographs, one such

change being the so-called "loss" of duodenal folds. However, over the last 2 decades it has been recognized that a number of changes in the duodenum clearly associated with celiac disease can be identified endoscopically. Because it is now understood that the manifestations of celiac disease are wide and variable, and that the disease is more common than recognized in the past, the clinical significance of these endoscopic observations has been greatly amplified. Awareness of these endoscopic features may alert the endoscopist to the presence of celiac disease and the need for duodenal biopsies in patients undergoing endoscopy for symptoms unrelated to the disease as well as those with vague, non-specific manifestations. The endoscopic features in the duodenum that are well-established as markers for celiac disease include: loss of folds, scalloping of folds and a mucosal mosaic pattern. Less commonly described findings include a visible vascular pattern and micronodularity in the duodenal bulb.

Although a radiologic loss of duodenum folds on barium studies had been noted with celiac disease by Nicollette and Tully in the 1970s,⁷⁰ the endoscopist demonstration was first reported by Brocchi et al. in 1988.⁷¹ These investigators described loss of folds in the duodenum, which they defined as no more than 3 folds in the second portion when viewed with maximal air insufflation. This finding had a sensitivity of 88% and specificity of 83% for the diagnosis celiac disease in 65 consecutive patients known or suspected to have the disease. McIntyre et al.⁷² noted that "loss of folds," defined as an obvious reduction in height or number, had a sensitivity of 73% and specificity of 97% for the diagnosis of celiac disease in 75 patients undergoing endoscopy because of a suspicion of celiac disease.

Jabbari et al.⁷³ reported in 1988 that the normally smooth duodenal folds had a scalloped appearance when viewed (en face) or in profile in many patients with celiac disease. This finding was best visualized on close inspection with maximal air insufflation. These investigators found that 22 of 28 consecutive patients with diagnosed celiac disease had scalloping of the duodenal folds. In a study of 73 children suspected to have celiac disease, Corazza et al.⁷⁴ noted that scalloping had a sensitivity of 88% and specificity of 87% for the diagnosis of subtotal villous atrophy. Grooves in the mucosa between folds have also been associated with celiac disease and are likely a manifestation of the same process that leads to scalloping.⁷⁵ Scalloping occurs when multiple grooves run over the apex of a duodenal fold (Fig. 3).

Scalloping itself is not specific for celiac disease. Shah et al.⁷⁶ described 13 cases in which scalloping



Figure 3. Endoscopic view of jejunum in same patient as Figure 1 showing scalloping of folds.

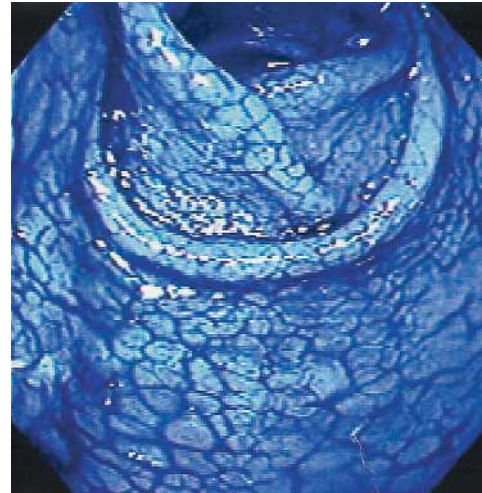


Figure 4. Endoscopic view of jejunum after spraying methylene blue dye solution in same patient as Figure 1 showing mucosal mosaic pattern.

of duodenal folds was not caused by celiac disease. In these cases, scalloping was attributed to human immunodeficiency virus–related infection in 6 patients, tropical sprue in 4, giardiasis in 1, and eosinophilic gastroenteritis in 1. In one patient, the duodenal biopsy was interpreted as normal. A case of duodenal scalloping caused by amyloidosis has also been reported.⁷⁷

Stevens and McCarthy⁷⁸ in 1976 described the presence of a mosaic mucosal pattern in the duodenal bulb, noted after spraying indigo carmine dye, in patients with celiac disease (Fig. 4). Subsequently, Jabbari et al.⁷³ noted that a mosaic mucosal pattern could be observed in the second portion of the duodenum without the benefit of chromoendoscopy.

The first systematic study of the endoscopic features of celiac disease is that of Maurino et al.,⁷⁹ which included 100 consecutive patients referred specifically for endoscopy to obtain intestinal biopsy specimens. The endoscopic signs evaluated included mosaic mucosal pattern (without dye spraying), scalloping, a loss of folds (fewer than 4), and visualization of underlying blood vessels. A mosaic mucosal pattern was observed in 14 of 36 (39%) patients with the histopathologic diagnosis of severe villous atrophy. In these 36 patients, loss of folds was noted in 27 (75%), scalloping in 12 (33%) and visualization of underlying blood vessels in 5 (14%). The presence of at least 1 endoscopic feature had a sensitivity of 94% and specificity of 92% for the diagnosis of celiac disease. Chromoendoscopy using a vital dye was shown by Niveloni et al.⁸⁰ to provide no additional benefit compared with simple endoscopic inspection alone in the identification with either the mosaic mucosal pattern or scalloping in 167 patients referred to obtain intestinal biopsy specimens.

Stevens and McCarthy⁷⁸ and Jabbari et al.⁷³ noted a prominence of underlying duodenal blood vessels in patients with celiac disease. Subsequently, studies by Maurino et al.,⁷⁹ Niveloni et al.,⁸⁰ and Dickey and Hughes⁸¹ found the sensitivity of this endoscopic sign to be, respectively, only 2%, 5%, and 14% in patients undergoing endoscopy to obtain small bowel biopsy specimens. Thus, prominence of submucosal blood vessels is the least sensitive endoscopic marker in all studies in which it was specifically evaluated.

In most patients, endoscopic abnormalities associated with celiac disease have been noted in the descending duodenum. Brocchi et al.,⁸² however, noted micronodularity in the bulb in a 14-year-old patient with celiac disease without associated abnormalities in the second portion of the duodenum.

There are several studies in which the utility of the endoscopic markers collectively has been evaluated in patients suspected to have celiac disease. That of Dickey and Hughes⁸¹ assessed mosaic or nodular mucosal pattern, scalloping, loss of folds, and visualization of underlying vessels. Villous atrophy was confirmed histopathologically in a total of 129 patients. The presence of at least one endoscopic marker had a sensitivity of 77%. The sensitivities for individual markers were as follows: scalloping, 57%; mosaic pattern, 53%; loss of folds, 16%; nodular mucosa, 9%; and visualization of underlying vessels, 2%. Niveloni et al.⁸⁰ evaluated loss of folds, scalloping, mosaic pattern, and visualization of underlying blood vessels in 167 patients who underwent endoscopy to obtain small bowel biopsy specimens. The presence of one or more endoscopic markers had a sensitivity and specificity of, respectively, 94% and

99% for the presence of celiac disease. Mosaic pattern was the most sensitive marker (89%) followed by scalloping (86%), loss of folds (44%), and visualization of submucosal vessels (5%).

Although it is interesting to note the presence of duodenal abnormalities in patients undergoing endoscopy to obtain intestinal biopsy specimens, of greater interest is the sensitivity and specificity of these markers for unrecognized celiac disease when the diagnosis has not been entertained.

Dickey⁸³ assessed 500 patients undergoing open access endoscopy for the presence of mosaic mucosal pattern, reduction in the number of folds, and scalloping in the duodenum. Specimens were obtained only if one or more of these abnormalities was found. Of 10 patients with at least one abnormality, 8 had villous atrophy.

Bardella et al.⁸⁴ prospectively studied 517 patients with dyspeptic symptoms as the indication for endoscopy. The markers assessed were loss or reduction in folds, mosaic or diffuse micronodular mucosal pattern, and scalloping. Four biopsy specimens were obtained from the second portion of the duodenum in all patients. At least one endoscopic finding was present in 5 patients, 3 of whom had villous atrophy confirmed histopathologically. Moreover, 3 patients in whom the endoscopic examination of the duodenum was normal had a specimen that was interpreted as consistent with celiac disease. Therefore, the presence of at least one endoscopic marker had a sensitivity of 50% and specificity of 99.6% for the presence of villous atrophy.

Dickey and Hughes⁸⁵ assessed the descending duodenum in 150 consecutive patients referred for endoscopy because of upper GI symptoms or iron deficiency anemia. Markers evaluated were nodular or mosaic mucosal pattern, scalloping, and reduction in number of folds. Three biopsy specimens were obtained in all patients irrespective of the findings at endoscopy. At least one endoscopic marker was present in 7 patients (5%), all of whom had villous atrophy. One patient in whom the duodenum appeared normal at endoscopy had villous atrophy. Of the 7 patients with endoscopic markers, a mosaic pattern was seen in 6, scalloping in 6, and a reduction in folds in 4. The overall sensitivity and specificity of the endoscopic markers for the presence of celiac disease were, respectively, 87.5% and 100%.

The presence or absence of endoscopic markers for celiac disease was determined by a single experienced endoscopist in the majority of reported studies. Inasmuch as these observers were presumably aware of the design and aims of the studies, and therefore searched specifically for certain findings, the question arises as to whether the endoscopic

markers are useful and readily recognized in routine clinical practice. Niveloni et al.⁸⁰ addressed this issue by studying interobserver agreement for recognition of scalloping, mosaic pattern, loss of folds, and visible vascular pattern. Using selected videotape recordings showing positive endoscopic findings as well as videotapes from control patients, Niveloni et al.⁸⁰ found interobserver agreement to be excellent for recognition of a mosaic pattern ($\kappa = 0.76$) and scalloping ($\kappa = 0.83$) among 5 independent endoscopists. Interobserver agreement was less for loss of folds ($\kappa = 0.41$).

In summary, a number of studies have demonstrated a strong correlation between the endoscopic duodenal findings of scalloping of folds, loss of folds, mosaic mucosal pattern, and a visibility of underlying blood vessels and the presence of celiac disease. These endoscopic findings have been found to be less sensitive for celiac disease in patients undergoing endoscopy for reasons other than a suspicion of celiac disease. However, given their high specificity, the recognition of any of these features should always prompt the endoscopist to obtain duodenal biopsy specimens. Furthermore, absence of these features does not exclude celiac disease and specimens should always be obtained when there is a suspicion that the disease may be present.

COMPLICATIONS

There is a growing body of data that suggests that early diagnosis and treatment can prevent complications of celiac disease including lymphoma, diabetes mellitus, cerebral calcification with epilepsy, osteopenia, and infertility.⁸⁶⁻⁹⁰ The mortality rate for patients with celiac disease is almost twice that of the general population, with most of the increase in mortality being caused by lymphoproliferative disease.⁹¹

There is an increased incidence of malignancy in patients with celiac disease, especially intestinal T-cell lymphoma, often referred to as enteropathy associated T-cell lymphoma (EATL).⁸⁶ EATL is 4- to 100-fold more common in patients with celiac disease. Adherence to a gluten-free diet can significantly reduce this risk.⁸⁶ In EATL the intraepithelial lymphocyte (IEL) population is CD3-, CD8- and has a clonal TcR rearrangement in both the lymphomatous bowel and in the adjacent nonlymphomatous bowel. This suggests that EATL evolves from the IEL through low-grade lymphoma to a high-grade tumor and may be neoplastic from the onset.^{92,93} EATL can present as a solid tumor that perforates easily or as multifocal involvement of the bowel with insidious weight loss and abdominal pain. Diagnosis can be difficult; contrast radiography and endoscopy are often inconclusive and

laparotomy may be required. Prognosis is poor with a 5-year survival rate of 10%.⁹⁴ Although there are case reports of endoscopic diagnosis, EATL is almost always diagnosed at surgery or autopsy because most patients present with perforation or obstruction.⁹⁴⁻⁹⁶ There are currently no established recommendations regarding screening or surveillance. In a prospective study, push enteroscopy in 23 patients with celiac disease responsive to dietary restrictions and 8 patients with refractory disease failed to detect any case of intestinal lymphoma, although 4 of the 8 patients with refractory disease were found to have ulcerative jejunitis.⁶⁹

Carcinoma of esophagus, mouth, pharynx, and small bowel are rarer complications of celiac disease.^{91,97} Ulcerative jejunoileitis presents with chronic multiple ulcers in the jejunum, ileum, and colon. These may perforate, bleed, or form strictures.⁹⁸ As with EATL, ulcerative jejunoileitis has an aberrant IEL population and it is thus important in patients with this finding to rule out lymphoma.

SUMMARY

Celiac disease is more common than previously recognized. The range of possible presenting manifestations is wide and includes iron deficiency anemia. Thus, endoscopists must be aware of the range of endoscopic manifestations of the disease, which are often subtle. Recognition of these characteristic endoscopic features may identify patients with previously unsuspected celiac disease including patients who are asymptomatic. Moreover, the increased awareness of the highly variable symptoms of celiac disease and advances in serologic testing will likely increase the number of patients referred for endoscopy to obtain small bowel biopsy specimens. The use of proper endoscopic technique for procuring specimens is essential for an accurate diagnosis.

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