

Common signs and symptoms, and a diagnosis that is often overlooked

Appropriate treatment of this underdiagnosed disease can resolve patient symptoms quickly and minimize the risk of complications. The trick is to consider the condition to begin with.

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CASES

Two patients presented to a gastroenterology office with common complaints. The first was a 27-year-old white female seeking an opinion regarding a 2-year history of chronic constipation. The patient believed she was likely suffering from irritable bowel syndrome (IBS). She had been taking polyethylene glycol (MiraLax) daily for the past year, which seemed to control her symptoms. She was concerned, however, about the continued use of MiraLax and about the need for a workup to investigate her constipation.

The patient admitted to generalized abdominal discomfort associated with the constipation and to a history of anal fissures. She also admitted to a history of headaches and aphthous ulcers. She denied hematochezia or any systemic symptoms and was generally healthy. Her family history was significant for a sister with type 1 diabetes mellitus. The patient did not smoke and rarely drank alcohol. The physical examination was remarkable only for some mild tenderness to palpation in the lower abdomen.

The evaluation included a CBC, complete metabolic panel, thyroid-stimulating hormone, and celiac disease comprehensive panel, which included an IgA tissue transglutaminase (tTG) antibody (Ab) level and an IgA endomysial (EMA) Ab titer. The results demonstrated an elevated IgA tTG Ab level and a high IgA EMA Ab titer, supporting a diagnosis of celiac disease. Other test results were within normal limits. With the presumptive diagnosis of celiac disease, the patient implemented a gluten-free diet and, within 4 weeks, her symptoms had nearly resolved.

The second patient was a 44-year-old female who presented for evaluation of iron deficiency anemia. The anemia had been chronic for approximately 10 years, and the patient's hemoglobin level remained between 8 and 9 g/dL unless she was taking supplemental iron. During iron supplementation, the patient's hemoglobin level was as high as 12 g/dL; however, she found it difficult to comply with therapy because the iron supplement caused GI side effects, primarily constipation.

The patient denied any melena, hematochezia or change in bowel habits. She had undergone digital rectal examination 10 months earlier, and stool guaiac testing was negative for occult blood. Her menstrual periods were regular and not particularly heavy. She admitted to occasional arthralgias and fatigue but denied any other significant complaints. In addition to iron, the patient was taking OTC ibuprofen, 200 mg twice daily as needed for arthralgias.

Past illnesses included a remote history of cervical cancer treated with cryosurgery. The patient's family history was noncontributory. She did not smoke and rarely drank alcohol. The physical examination was remarkable only for pale conjunctivae.

This patient's initial workup included iron studies and celiac disease antibody testing. The results confirmed the iron deficiency and revealed a high IgA tTG Ab level, strongly suggesting a diagnosis of celiac disease. The



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patient subsequently underwent esophagogastroduodenoscopy (EGD) with small bowel (duodenal) biopsies. Biopsy findings, which revealed intraepithelial lymphocytosis and subtotal villous atrophy, confirmed the celiac disease diagnosis.

Because of the risk of bone loss associated with celiac disease, the patient also underwent dual energy x-ray absorptiometry, which demonstrated osteopenia. She was advised to begin a gluten-free diet and calcium and vitamin D supplementation. Additionally, she was prescribed an alternative iron supplement, Chromagen, which she tolerated. The patient's bone density and nutritional status are now appropriately monitored.

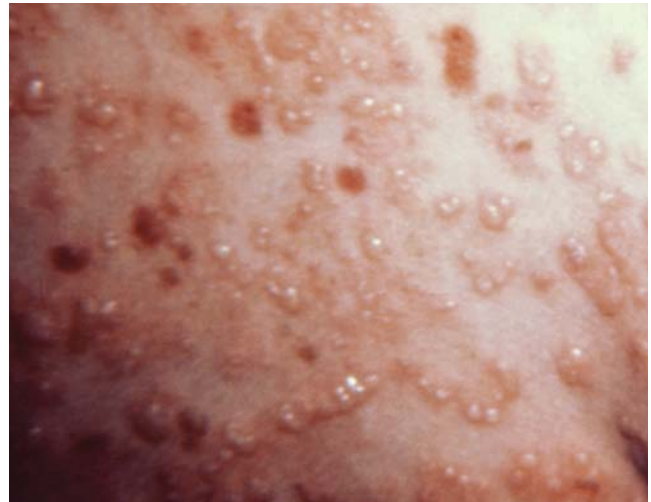
DISCUSSION

Celiac disease, also referred to as gluten enteropathy or gluten sensitive enteropathy, is an immune-mediated disease of the small intestine that is precipitated by the ingestion of gluten, a protein derived from wheat, barley, and rye. In genetically predisposed individuals, exposure to dietary gluten causes damage to the small intestinal mucosa that can cause malabsorption of nutrients and a broad range of GI and extraintestinal clinical manifestations.

Classically, celiac disease is recognized during infancy when patients manifest typical symptoms associated with malabsorption that include diarrhea, steatorrhea, and weight loss. In recent years, however, the disease is frequently being diagnosed in adolescents and adults in whom atypical or subclinical presentations may predominate.^{1,2} The two cases reported here exemplify such presentations.

Once considered rare in the United States, celiac disease affects between 1 in 100 and 1 in 250 Americans.^{3,5} Although it is considered more common in people of Northern European ancestry, a recent study found a similar disease prevalence among whites and minority groups (Asians, African Americans, Hispanics) in the United States.⁴ The prevalence is higher in first-degree (10%) and second-degree relatives of patients with celiac disease and in other groups considered high-risk.^{3,6}

Factors that place a person at high risk include conditions that may result from celiac disease, such as iron deficiency anemia, and by conditions strongly associated with the dis-



CDC

FIGURE 1. Dermatitis herpetiformis

ease, such as Down syndrome, type 1 diabetes mellitus, and autoimmune thyroid disease.⁶ Notably, autoimmune diseases occur more frequently in patients with celiac disease.⁷ Potentially serious complications of celiac disease in adults include a modest increase in the risk of GI cancers and non-Hodgkin's lymphoma.^{8,9} Strict adherence to a gluten-free diet, however, may reduce the malignancy risk to approximately that of the overall population.¹⁰

In contrast to presenting classically with diarrhea, many patients with celiac disease may be asymptomatic or report atypical GI symptoms such as constipation, abdominal pain, nausea, or lactose intolerance.^{1,4,11} Extraintestinal clinical manifestations can occur in the absence of GI symptoms and include iron deficiency anemia, recurrent aphthae, vitamin D and calcium deficiency, osteoporosis, elevated liver function test results, infertility, and neurologic disorders.^{2,12,13} Dermatitis herpetiformis, a pruritic papulovesicular rash characteristic of celiac disease, occurs in approximately 10% of patients¹¹ (Figure 1).

Most patients with celiac disease never receive a diagnosis,¹⁴ and in those who do, the mean duration of symptoms before diagnosis is 11 years.¹¹ Among adults, the disease is approximately 3 times more prevalent in women^{1,11} and, not

TEACHING POINTS

- Instead of having diarrhea, many patients with celiac disease may be asymptomatic or report atypical GI complaints such as constipation, abdominal pain, or lactose intolerance.
- A substantial number of patients with celiac disease initially receive a diagnosis of irritable bowel syndrome.
- Most patients with celiac disease never receive a diagnosis.
- Complications associated with celiac disease include iron deficiency anemia, osteoporosis, and a modest increase in the risk of GI cancers and non-Hodgkin's lymphoma.
- All diagnostic testing should be performed while the patient remains on a gluten-containing diet.
- Treatment for celiac disease can alleviate symptoms, reverse nutritional deficiencies, improve bone mineral density, and minimize the risk of associated malignancy.

CASE REPORT | Celiac disease

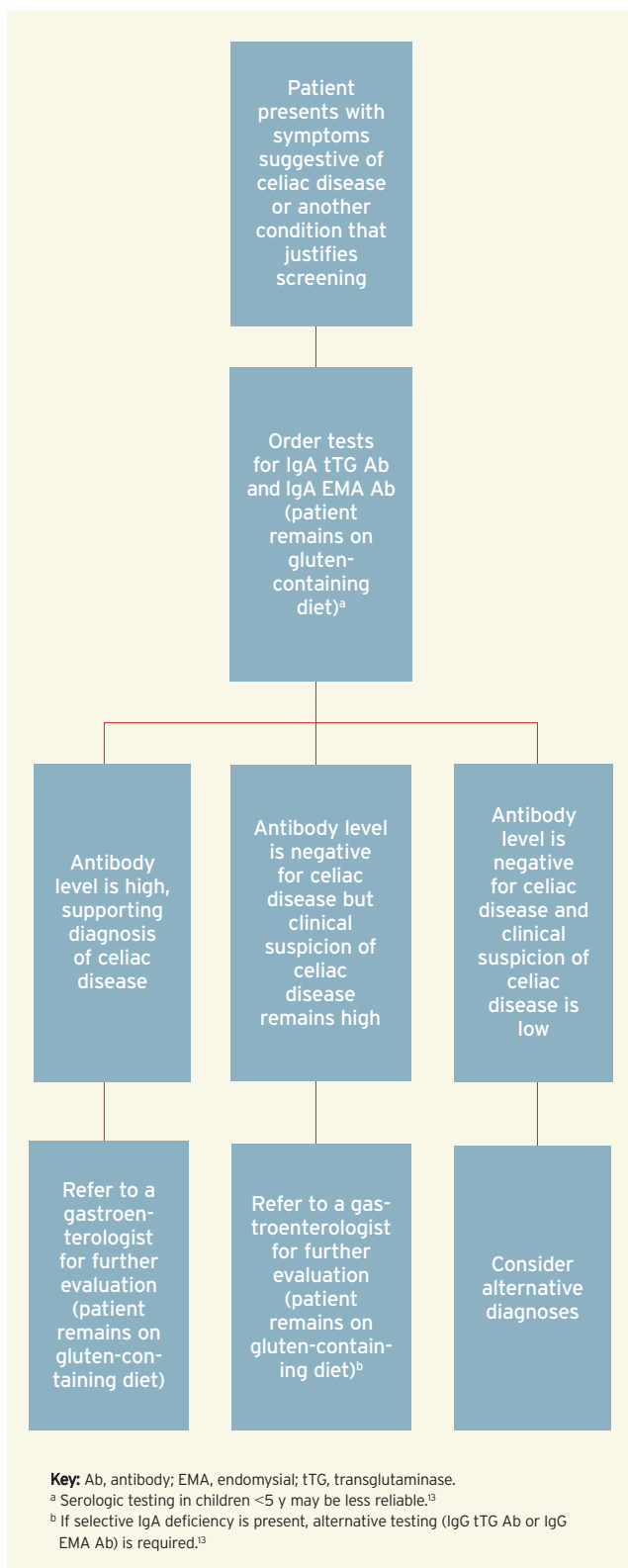
TABLE 1. Gluten-free and gluten-containing foods

Food group	Do not contain gluten	May contain gluten	Contain gluten
Milk & milk products	Whole, low-fat, skim, dry, evaporated, or condensed milk; buttermilk; cream; whipping cream; Velveeta cheese food; American cheese; all aged cheeses, such as cheddar, Swiss, Edam, and Parmesan	Sour cream, commercial chocolate milk and drinks, nondairy creamers, all other cheese products, yogurt	Malted drinks
Meat or meat substitutes	100% meat (no grain additives); seafood; poultry (breaded with pure cornmeal, potato flour, or rice flour); peanut butter; eggs; dried beans or peas; pork	Meat patties; canned meat; sausages; cold cuts; bologna; hot dogs; stew; hamburger; chili; commercial omelets, soufflés, fondue; soy protein meat substitutes	Croquettes, breaded fish, chicken loaves made with bread or bread crumbs, breaded or floured meats, meatloaf, meat balls, pizza, ravioli, any meat or meat substitute, rye, barley, oats, gluten stabilizers
Breads & grains	Cream of rice; cornmeal; hominy; rice; wild rice; gluten-free noodles; rice wafers; pure corn tortillas; specially prepared breads made with corn, rice, potato, soybean, tapioca, arrowroot, carob, buckwheat, millet, amaranth, and quinoa flour	Packaged rice mixes, cornbread, ready-to-eat cereals containing malt flavoring	Breads, buns, rolls, biscuits, muffins, crackers, and cereals containing wheat, wheat germ, oats, barley, rye, bran, graham flour, malt; kasha; bulgur; Melba toast; matzo; bread crumbs; pastry; pizza dough; regular noodles, spaghetti, macaroni, and other pasta; rusks; dumplings; zwieback; pretzels; prepared mixes for waffles and pancakes; bread stuffing or filling
Fats & oils	Butter, margarine, vegetable oil, shortening, lard	Salad dressings, nondairy creamers, mayonnaise	Gravy and cream sauces thickened with flour
Fruits	Plain, fresh, frozen, canned, or dried fruit; all fruit juices	Pie fillings, thickened or prepared fruit, fruit fillings	None
Vegetables	Fresh, frozen, or canned vegetables; white and sweet potatoes; yams	Vegetables with sauces, commercially prepared vegetables and salads, canned baked beans, pickles, marinated vegetables, commercially seasoned vegetables	Creamed or breaded vegetables; those prepared with wheat, rye, oats, barley, or gluten stabilizers

Food group	Do not contain gluten	May contain gluten	Contain gluten
Snacks & desserts	Brown and white sugar, rennet, fruit whips, gelatin, jelly, jam, honey, molasses, pure cocoa, fruit ice, carob	Custards, puddings, ice cream, ices, sherbet, pie fillings, candies, chocolate, chewing gum, cocoa,	Cakes, cookies, doughnuts, pastries, potato chips, popcorn, dumplings, ice cream cones, pies, prepared cake and cookie mixes, pretzels, bread pudding
Beverages	Tea, carbonated beverages (except root beer), fruit juices, mineral and carbonated waters, wines, instant or ground coffee	Cocoa mixes, root beer, chocolate drinks, nutritional supplements, beverage mixes	Postum, Ovaltine, malt-containing drinks, cocomalt, beer, ale
Soups	Those made with allowed ingredients	Commercially prepared soups, broths, soup mixes, bouillon cubes	Soups thickened with wheat flour or gluten-containing grains; soup containing barley, pasta, or noodles
Thickening agents	Gelatin, arrowroot starch; corn flour, germ, or bran; potato flour; potato starch flour; rice bran and flour; rice polish; soy flour; tapioca, sago		Wheat starch; all flours containing wheat, oats, rye, malt, barley, or graham flour; all-purpose flour; white flour; wheat flour; bran; cracker meal; durham flour; wheat germ
Condiments	Gluten-free soy sauce, distilled white vinegar, olives, pickles, relish, ketchup	Flavoring syrups (for pancakes or ice cream), mayonnaise, horseradish, salad dressings, tomato sauces, meat sauce, mustard, taco sauce, soy sauce, chip dips	
Seasonings	Salt, pepper, herbs, flavored extracts, food coloring, cloves, ginger, nutmeg, cinnamon, bicarbonate of soda, baking powder, cream of tartar, monosodium glutamate meat extracts	Curry powder, seasoning mixes, meat extracts	Synthetic pepper, brewer's yeast (unless prepared with a sugar molasses base), yeast extract (contains barley)
Prescription products		All medicines: check with pharmacist or pharmaceutical company	

Adapted with permission from Gluten-free diet. Jackson-Siegelbaum Gastroenterology. <http://gicare.com/diets/Gluten-Free.aspx>. Accessed November 18, 2009.

ALGORITHM. Diagnosis of celiac disease



surprisingly, a substantial number of patients receive a diagnosis of IBS before the celiac disease is identified.^{1,11} In one study, before treatment was initiated, nearly 50% of patients' presenting symptoms were consistent with the Rome II criteria for IBS.¹

Establishing the diagnosis of celiac disease generally requires positive serologic testing; characteristic duodenal biopsy findings, which include intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy; and a positive response to a gluten-free diet^{6,13} (Figure 2). In the primary care setting, serologic screening can best be accomplished by ordering tests of IgA EMA Ab or IgA tTG Ab.^{6,15} Laboratories may also offer celiac disease panels that include multiple antibody tests.

According to current recommendations, patients with positive serologic test results should be referred to a gastroenterologist for EGD with duodenal biopsy, the gold standard for diagnosis^{6,13} (see Algorithm: Diagnosis of celiac disease). Some have suggested that, because of the high sensitivity and specificity of IgA tTG and IgA EMA antibody tests, duodenal biopsy may not be necessary in all cases.^{16,17} Consultation with a gastroenterologist may be warranted in every case, however. A gluten-free diet is expensive, complicated, and difficult to follow (Table 1). Additionally, further testing may be required to monitor a patient's disease course.

Referral to a gastroenterologist should also be considered when initial serologic test results are negative but suspicion for celiac disease remains high. Patients with selective IgA deficiency, a condition much more common in persons with celiac disease than in the general population,¹⁸ may have a negative IgA Ab serologic test result and require alternative serologic screening with an IgG tTG or IgG EMA Ab test. Additionally, when initial serologic screening is negative, establishing the diagnosis may require duodenal biopsies.^{6,13}

All diagnostic testing should be performed while the patient remains on a gluten-containing diet, as serologic and histologic findings may resolve after the institution of a gluten-free diet.⁶ Once testing is complete, the diagnosis of celiac disease is further confirmed by a patient's positive response to a gluten-free diet.¹³

CONCLUSION

The overall management of celiac disease requires patient education, adherence to a gluten-free diet, consultation with a dietitian, and long-term clinical follow-up^{6,13} (Table 2). Because strict lifelong adherence to a gluten-free diet is so challenging, referral to a support group is also recommended.⁶ A number of online resources—for example, the Celiac Sprue Association—provide educational material and may assist physician assistants and patients in complying with treatment recommendations.

Once gluten is eliminated from the diet, most patients will have noticeable improvement of symptoms within days or weeks.¹⁸ Continued follow-up care should include treatment of iron, folic acid, calcium, and vitamin D deficiencies and evaluation for osteoporosis.^{6,13} Clinicians should also moni-

tor dietary compliance and periodically assess patients for potential complications.¹³ Because of the risk of GI malignancy, the development of alarm symptoms such as abdominal pain, diarrhea, and weight loss despite a gluten-free diet should prompt further investigation.¹⁸

Manifestations of celiac disease range from asymptomatic to severe, including the consequences of malabsorption. As demonstrated in the two reported cases, many patients present with atypical complaints. Even for those who do not exhibit nutritional deficiencies, identification and treatment of celiac disease can significantly improve quality of life and may prevent future complications.

Celiac disease is not uncommon in this country,^{3,5} yet it remains widely unrecognized.¹¹ The diagnosis should be considered in patients who present with compatible symptoms, typical or atypical, and in those with other indications for screening. Treatment for celiac disease can alleviate symptoms, reverse manifestations such as nutritional deficiencies, improve bone mineral density, and minimize the risk of associated malignancy.⁶ Broader recognition of the disease will thus likely produce improved outcomes for a substantial number of patients. **JAAPA**

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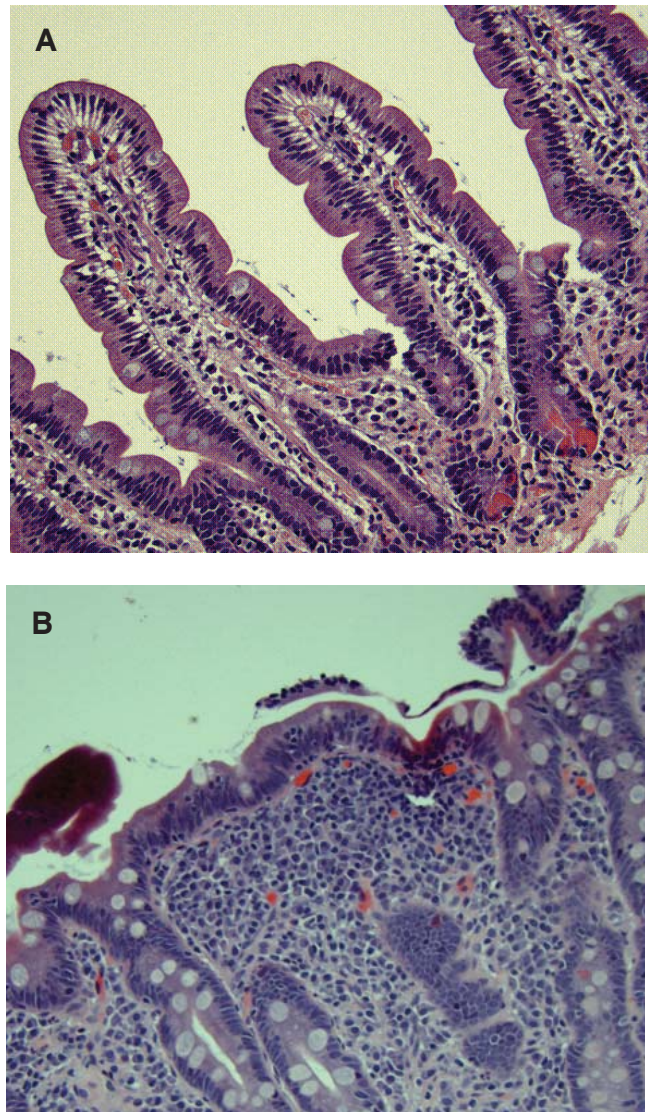


FIGURE 2. Microscopic views of small bowel biopsies show normal small intestine fingerlike villi and crypts (a); and flat celiac mucosa with hyperplastic crypts and complete loss of normal villous architecture (b).

TABLE 2. Key elements in the management of patients with celiac disease

Consultation with a skilled dietitian
Education about the disease
Lifelong adherence to a gluten-free diet
Identification and treatment of nutritional deficiencies
Access to an advocacy group
Continuous long-term follow-up by a multidisciplinary team

Data from NIH Consensus Development Conference Statement on Celiac Disease.¹³