CASE REPORT

Celiac disease unmasked by acute severe iron deficiency anemia

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The prevalence of celiac disease (CD) appears to be increasing in the United States. However, the proportion of new CD cases with atypical presentations is also rising. We present the case of a 49-year-old woman who was diagnosed with CD in the setting of new, severe iron-deficiency anemia, 13 years into treatment of diarrhea-predominant irritable bowel syndrome associated with chronic mildly elevated liver function tests. While CD and iron deficiency anemia are common, this is a rare presentation of CD.

Keywords: iron deficiency anemia; celiac disease; irritable bowel syndrome; elevated liver enzymes

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Celiac disease (CD) has been diagnosed in 7–8% of patients thought to have irritable bowel syndrome (IBS) (1), with variable lag times. The case below illustrates an extended delay in confirming CD in such a patient given its atypical presentation.

Case description

A 49-year-old Caucasian female was found to have acute iron deficiency anemia (see Table 1) when she presented to the gastroenterology clinic for routine follow-up of gastroesophageal reflux disease, IBS, and abnormal liver enzymes. She had had IBS with diarrhea for at least 13 years that was resistant to treatment; diarrhea was mucoid, intermittent, and associated with abdominal bloating, sense of incomplete evacuation, and relief of bloating and cramping with bowel movements. She denied having fevers, chills, night sweats, weight loss, constipation, melena, hematochezia, hematemesis, vomiting, dysphagia, jaundice, acholic stools, dark urine, hematuria, pruritus, easy bruising, chest pain, or shortness of breath. Her other comorbidities included well-controlled diabetes mellitus, hypertension, dyslipidemia, cholelithiasis, morbid obesity, and depression. The patient did not use alcohol or intravenous drugs and had never smoked. She had allergies to meclizine and sulfa antibiotics and was intolerant of tramadol. Her family history was non-contributory. Her medications included chlordiazepoxide–clidinium 2.5–5 mg four times daily, glipizide 10 mg twice daily, metformin 1,000 mg twice daily, pravastatin 40 mg daily, irbesartan 75 mg daily, naproxen 500 mg twice daily, venlafaxine 150 mg daily, a daily multivitamin, and pantoprazole 40 mg twice daily.

Her vital signs and physical examination were normal except for morbid obesity; her abdomen was soft, nontender, and non-distended, with normal bowel sounds and negative Murphy sign.

Esophagogastroduodenoscopy (EGD) 2 years prior showed a normal duodenum, erosive gastropathy but no Helicobacter pylori, and Grade I esophageal varices. The liver enzyme abnormalities (see Table 2) were mild and had been attributed to fatty liver disease in the setting of compatible sonographic findings as well as negative viral hepatitis screen, ceruloplasmin, antimitochondrial antibody, and alpha-1 antitrypsin level. She had been offered a liver biopsy 4 years prior but declined it. Work-up for diarrhea that included stool studies, colonoscopy with biopsies, and a small bowel series had been non-diagnostic, as was computerized tomography (CT) of her abdomen.

The patient was thus scheduled for elective endoscopy for further evaluation of anemia. EGD showed a superficial gastric ulcer with no stigma of bleeding in the gastric antrum, 8 mm in largest dimension, a normal duodenum, Grade I esophageal varices, and no H. pylori. Colonoscopy was normal.

Her gastric ulcer was attributed to chronic use of non-steroidal anti-inflammatory drugs for abdominal pain. However, she developed lightheadedness the day
after endoscopy and was admitted to a different hospital. She was resuscitated with intravenous fluids and blood transfusion.

At a post-hospital visit to our clinic, capsule endoscopy was ordered as prior work-up of her anemia was inconclusive. Given the long history of uncontrolled IBS-like symptoms, chronic mildly elevated LFTs, and severe iron deficiency anemia with possible occult gastrointestinal bleeding, the possibility of CD was entertained, so a CD panel was requested.

Transglutaminase Ab (TgA) was 82 (reference range <4) U/mL and serum immunoglobulin A was 525 (reference range: 81–463) mg/dL. Capsule endoscopy did not show any evidence of bleeding but revealed loss of folds of duodenal mucosa, villous atrophy, and scalloping, suggestive of CD. EGD was repeated; patchy erythema was seen in the gastric antrum. The second part of the duodenum appeared normal, but biopsy confirmed mucosal subtotal villous blunting with intraepithelial lymphocytosis, compatible with active CD, Marsh type IIIB. A gluten-free diet (GFD) was recommended. Her compliance led to normalization of TgA levels (see Table 2) with subsequent resolution of her IBS-like symptoms and normalization of her transaminases (Table 3).

**Discussion**

CD is a gluten-dependent, immune-mediated disorder primarily affecting small intestinal mucosa. The prevalence of CD in the United States has been estimated at 1% (2). Although the incidence of CD has increased recently, a higher proportion of cases does not present with diarrhea and weight loss – typical symptoms of the disease (3). The spectrum of possible presentations of CD is wide and overlaps with irritable bowel disease and several other conditions (4); therefore, CD diagnoses have often been wrongly applied (5) or delayed. IgA anti-tissue transglutaminase (TTG) antibody has 95% sensitivity and 95% specificity for diagnosis of CD and is the preferred single test (4). When CD is suspected (based on TgA elevation), multiple duodenal biopsies are strongly recommended to confirm the diagnosis; the Marsh classification can be applied to positive histological findings. These tests should be performed while patients are on a gluten-containing diet.

Liver disease associated with CD is possibly attributable to one or more of several pathways, including chronic inflammation, small intestine bacterial overgrowth, genetic predisposition, gut permeability, and molecular mimicry (6). Such liver disease may present as non-alcoholic steatohepatitis, primary biliary cirrhosis, or autoimmune hepatitis. Liver abnormalities are often ameliorated by adherence to a GFD, especially in the absence of morbid obesity (7).

Iron deficiency is one of several nutritional maladies associated with CD, to which obesity has also been

| Parameter with normal value                       | Baseline, 22 months prior to diagnosis | Presentation/diagnosis of CD | 13 months after starting GFD |
|---------------------------------------------------|---------------------------------------|-----------------------------|-----------------------------|
| White blood count (3.6–11 K/μL)                   | 9.2                                   | 6.1                         | 10.4                        |
| Hemoglobin (12–16 g/dL)                           | 12.0                                  | 8.1                         | 14.4                        |
| Hematocrit (35–47%)                               | 36.1                                  | 25.7                        | 42.3                        |
| Platelets (150–400 K/μL)                          | 163                                   | 188                         | 143                         |
| Red cell distribution width (11–15%)              | 14.0                                  | 21.2                        | 14.8                        |
| Mean corpuscular volume (80–100 fl)               | 89.5                                  | 75.7                        | 95.2                        |
| Mean corpuscular hemoglobin (26–34 pg)            | 29.7                                  | 23.9                        | 32.4                        |
| Mean corpuscular Hemoglobin concentration (32–36 g/dL) | 33.2                                  | 31.6                        | 34.1                        |

GFD, gluten-free diet.

| Time at the time of diagnosis | At the time of diagnosis | 7 months after starting GFD | 13 months after starting GFD |
|-------------------------------|--------------------------|-----------------------------|-----------------------------|
| Transglutaminase Ab (reference range <4 U/mL) | 82                        | 10                          | 5                           |

**Table 2. Transglutaminase antibody trend**

| Time at the time of diagnosis | At the time of diagnosis | 7 months after starting GFD | 13 months after starting GFD |
|-------------------------------|--------------------------|-----------------------------|-----------------------------|
| Transglutaminase Ab (reference range <4 U/mL) | 82                        | 10                          | 5                           |

| Normal value | 11 years prior to diagnosis | 3 years prior to diagnosis | 1 month prior to diagnosis | 7 months after starting GFD |
|-------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| AST (15–46 U/L) | 85                          | 94                          | 74                          | 44                          |
| ALT (13–69 U/L) | 65                          | 75                          | 40                          | 43                          |
| ALP (38–126 U/L) | 73                          | 123                         | 112                         | 105                         |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

**Table 3. Liver function tests**
linked (8). Iron deficiency anemia may be remedied by institution of GFD.

Aside from abnormal elevated liver enzymes and chronic iron deficiency with anemia, CD may also present with any of several atypical features. These include premature osteoporosis, peripheral neuropathy, thyroid disease, dermatitis herpetiformis, and oral aphthous ulcers, as well as incidental discovery of villous atrophy via endoscopy or histology (4).

IBS is the commonest misdiagnosis in CD patients (9); the prevalence of biopsy-proven CD can be four times higher among patients with IBS compared to controls without IBS (1). The American College of Gastroenterology thus recommends excluding CD in patients with IBS (4). The perceived overlap between CD and IBS may be complicated by non-celiac gluten sensitivity (NCGS), a group of conditions in which an adverse food reaction akin to CD follows gluten ingestion, yet tests for CD are negative or inconclusive (10). Considering that wheat contains gluten and carbohydrates (fructans), non-celiac wheat sensitivity may actually underlie IBS (11).

Can capsule endoscopy be substituted for biopsy in the diagnosis of CD? Current guidelines of American College of Gastroenterology only recommend this when a patient with positive initial serology is unwilling to have upper endoscopy and biopsy (4). The new guidelines of European Society of Gastrointestinal Endoscopy concur with this based on low-quality evidence (12). More research is needed in this area.

Conclusion

Several cases of CD present atypically. Clinicians should maintain a high index of suspicion for CD in settings of unexplained iron deficiency anemia. Additionally, the presence of at least 2 months of abdominal pain relieved by defecation and/or associated with a change in frequency and/or form of stool should alert the clinician to screen the patient for CD. Timely diagnosis of CD has the potential to reduce patient morbidity and healthcare costs.

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