Isolated Iron Deficiency: An Atypical Manifestation Of Celiac Disease

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A 38-year-old woman presented with iron-deficiency anemia in 1983. Eight years later, she developed classic symptoms of celiac disease, ie, diarrhea, weight loss, and diminished appetite. New noninvasive blood tests and the ease with which small bowel biopsies can be achieved are having an impact on the clinical pattern of the disease. This report includes a discussion of anemia as the presenting sign of celiac disease and a review of the literature.

Key words. Celiac disease; anemia, hypochromic.
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Celiac disease is a permanent intolerance to gliadin leading to intestinal villous flattening and crypt hyperplasia in susceptible subjects. Some cases have typical presentations, others have atypical clinical pictures but symptoms compatible with celiac disease, and a third group is composed of asymptomatic or "silent" patients.[1]

Celiac disease in adults may be diagnosed easily when classic features are present, but it may be overlooked for years when symptoms are mild or absent. In the past, atypical presentations were considered uncommon.[2-4]

The purpose of the present report is to describe an unusual presentation of the disease—iron deficiency anemia—and to review the changing patterns of adult celiac disease in view of the new noninvasive diagnostic tests available.

Case Report

In August 1983, a 38-year-old woman presented to our clinic complaining of fatigue. Her physical examination was unremarkable except for pallor and weight loss. She had no history of rectal bleeding or melena, and her iron intake and menses were normal. Laboratory evaluation revealed a hemoglobin of 10.2 g/dL (102 g/L); mean corpuscular volume, 69 fL; serum iron, 14 μg/dL (2.5 μmol/L); serum iron-binding capacity, 364 μg/dL (65 μmol/L); vitamin B_{12}, 150 pg/mL (111 pmol/L); and folic acid, 3.6 ng/mL (8 nmol/L). Thyroid, kidney, and liver function tests were all normal as were repeated tests for occult blood in her stool.

She had presented 3 years earlier with similar complaints, for which she had undergone repeated therapeutic trials with iron supplements that had produced no real effect on her hemoglobin or serum iron levels. As the patient refused invasive investigations, she was put on prolonged iron treatment with no effect.

In April 1988, she presented complaining of polyarthralgia and morning stiffness, but with no accompanying physical signs. Rheumatic factor, antinuclear antibodies, and complement levels were all normal or negative except for a high erythrocyte sedimentation rate. Radiologic examinations of the hands and cervical spine were normal, and her complaints resolved some months later without treatment.

One year later, 9 years after her initial complaints, she presented again with fatigue and loss of appetite and weight. She agreed to undergo tests for malabsorption, one of which was the D-xylose blood test. D-xylose is a five-carbon sugar usually absorbed in the duodenum and jejunum. Xylose is not completely metabolized, and therefore its excretion into urine or its concentrations in blood following a standardized dose can be used as a small

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intestinal absorption test. In our patient, the D-xylose blood test result was abnormal: 11% after 3 hours (normal >25%). Barium swallow with small intestinal follow-through and abdominal ultrasonography was normal.

A few months later, she developed diarrhea, nausea, and 7 kg of weight loss. She agreed to undergo endoscopy with small bowel biopsies, the reference standard for the diagnosis of celiac disease. The biopsies revealed villous atrophy, crypt hyperplasia, and lamina propria membranae inflammation, suggesting a diagnosis of celiac disease.

The patient was put on a gluten-free diet, after which she recovered completely from all symptoms and regained the weight she had lost. Today, 4 years after initiation of the diet, her hemoglobin is 14.6 g/dL (146 g/L); her serum iron is also normal. Repeated intestinal biopsies have shown normal villous architecture. Serum anti-endomysial antibody has been negative.

Discussion

The most common symptoms in patients with extensive celiac disease include diarrhea, flatulence, weight loss, and weakness. Anemia occurs in 40% to 90% of adults with severe disease.[5] It is usually caused by impaired absorption of iron or folate from the proximal intestine. Low serum iron or impaired folate absorption is found in 30% to 83% and in 95% to 100% of patients with the disease, respectively.[5–7]

Anemia as the only or presenting sign of the disease has been reported to be uncommon, occurring in between 12% and 20% of patients.[6] Logan et al[8] demonstrated the importance of two factors in the diagnosis of celiac disease in patients whose only symptom was anemia: physician alertness to atypical presentations of celiac disease, and the ease of obtaining biopsies. In their study, no cases of anemia as a presenting sign of celiac were found between 1960 and 1964, whereas 30% of recorded cases between 1975 and 1979 presented with anemia.[8] A retrospective study conducted at our institution between 1967 and 1984 revealed similar results.[9] Seventy-nine percent of patients had low serum iron and 87% had low serum folate, but weakness and anemia were the presenting signs in only 20% of patients. In some series, however, physicians who were alert to the possibility of atypical presentation have identified up to 44% of celiac patients presenting with anemia.[10]

In recent years, with the advent of sensitive, noninvasive blood tests such as IgA antigliadin or antiendomysial antibodies, and the ease with which biopsies can be obtained, the diagnosis of gluten sensitivity often depends on the presence of atypical or subtle abnormalities, such as anemia.[11] In a large proportion of cases, the condition may be virtually asymptomatic. On the other hand, patients with latent disease may present with clinical symptoms yet normal villous structure and only one histologic abnormality, such as enhanced villous intraepithelial lymphocyte population or a range of antibodies of the IgM and IgA subclasses in the jejunal luminal fluid. Both of these abnormalities, occurring either individually or in combination, are early signs of celiac disease.[11] It is well established that symptoms and degree and type of malabsorption are related to the total length of involved jejunum and the length of functional ileum remaining.[12]

Ferguson et al[13] proposed a two-stage model of the disease: latent and fully expressed. Early in the disease, inappropriate immunity, which occurs relatively frequently and is genetically restricted, manifests histologically as a high count of villous intraepithelial lymphocytes. At this stage, symptoms may also be extraintestinal (ie, skin, mouth, kidney, and joints). Our patient had guaiac-negative iron deficiency anemia and polyarthralgia. The fact that her stools were negative for occult blood suggested that her iron deficiency was not related to blood loss, but rather to a problem in iron absorption. Not surprisingly, since the problem was one of iron absorption rather than iron loss, supplements, which do not affect the disease, were ineffective at this stage. The only certain way to correct the anemia was by restoring the patient's villi by bringing her to remission.

In the second stage, overt enteropathy develops. The severity of this stage is generally enhanced in patients with intestinal infection, hyperpermeability episodes, nutrient deficiency, and other comorbid conditions.[13] It is during the early latent stage that symptoms, if present at all, are atypical. The use of a noninvasive test, such as for serum antiendomysial antibody, offers an easy means of investigating these patients and those with peculiar or resistant iron deficiency anemia.[14] Antiendomysial antibodies attack the membrane of smooth muscle bundles in primates. The IgA class of these antibodies was present in patients with celiac disease with almost 100% sensitivity and specificity.[15] The antibody titer correlates with disease activity and may disappear when the patient is in remission.

Sategna-Guidetti et al[5] evaluated changes in the pattern of clinical expression of adult celiac disease. They found that in the era of sensitive blood tests (1990–1992), there was an increased number of new diagnoses as compared with an earlier time frame (1987–1989). The development of sensitive blood tests has resulted in more patients being diagnosed with low serum iron but fewer with overt anemia. Diarrhea is less often the presenting symptom (43% as compared with 90% earlier); the main presenting symptoms are now usually abdominal pain (38%) and distention (25%).[5]

Physician alertness to unusual presentations of celiac disease combined with simple blood tests may totally change its clinical picture. In addition to screening for occult blood in stool samples, antiendomysial antibodies may become another routine investigative tool in patients with iron deficiency.

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