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Folate Insufficiency Due to Celiac Disease in a 49-Year-Old Woman of Southeast Asian-Indian Ethnicity

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ABSTRACT

The clinical presentation of celiac disease has evolved from chronic diarrhea and malnutrition to mild nutrient insufficiencies. Recently diagnosed adults with celiac disease should be assessed for micronutrient deficiencies because early institution of a gluten-free diet (GFD) prevents morbidity and reduces the incidence of gastrointestinal malignant neoplasms and osteoporosis. In this report, we present the case of a 49-year-old woman of Southeast Asian–Indian descent living in the United States who had folate insufficiency, as manifested by low serum and red blood cell (RBC) folate levels. Further investigation, including serologic testing and intestinal biopsy, confirmed a diagnosis of celiac disease and other nutrient deficiencies. Managing the condition of this patient with folate supplements and implementation of a recommended GFD reversed the folate insufficiency. In conclusion, when serum and/or RBC levels are low in a person of Southeast Asian-Indian descent living in a country with folate fortification of the grain supply, such as the United States, the medical team needs to look for an organic cause, as in our patient, to diagnose and manage celiac disease early and, hopefully, forestall complications.

Keywords: folate insufficiency, celiac disease, Southeast Asian Indian, gluten free diet, intraepithelial lymphocytes, villous blunting

Folate is an essential water soluble micronutrient that functions as a 1-carbon donor essential for nucleotide and amino-acid synthesis.[1] The major dietary sources of folate are green leafy vegetables and legumes. In 1998, to reduce intrauterine neural tube defects, the United States (US) Food and Drug Administration (FDA) required all cereal grain products to be fortified with folate.[1] This action resulted in an increase in dietary folate of 200 μg per day with a paralleled increase in plasma folate levels in the US population, resulting in a substantial decrease in dietary folate deficiency. Also, folate deficiency is uncommon in women of Southeast Asian–Indian (hereinafter, Asian Indian) descent who reside in the United States, with average plasma levels of 13.2 ng per mL at the upper end of the reference range.[2] Similarly, iron deficiency is very common in young women of Asian Indian descent who reside in India.[3] Hence, we report a case of an otherwise healthy 49-year-old woman of Asian Indian descent living in the United States who consumed a diet including vegetables but had low serum and red blood cell (RBC) folate levels. After she sought treatment because of vague gastrointestinal (GI) symptoms, her work-up revealed celiac disease as the cause.

Abbreviations

US, United States; FDA, United States Food and Drug Administration; RBC, red blood cell; GI, gastrointestinal; GERD, gastroesophageal reflux disease; BMI, body mass index; Ig, immunoglobulin; GFD, gluten-free diet; CCK, cholecystokinin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; MMA, monomethylamine; NA, not applicable; IgA, immunoglobulin A; ELIA, enzyme labeled anti-isotype assay; IgG, immunoglobulin G; TIBC, total iron-binding capacity

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Case History

A 49-year-old woman of Asian Indian descent sought treatment at the gastroenterology clinic of University of California Davis Medical Center, reporting early satiety with no loss of appetite for the past several years. She stated that despite maintaining fairly regular oral intake, she has not been able to gain weight. Also, she noted some intolerance

to fatty foods, which caused her to have looser bowel movements. She reported that typically she had 1 formed bowel movement per day; however, after a particularly fatty meal, she had had looser stools. She reported no nausea, heartburn, bloating, abdominal pain, gastroesophageal reflux disease (GERD) symptoms, dysphagia, hematochezia (rectal bleeding), or melena. On physical examination, there were no skin changes, pallor, or edema. However, the body mass index (BMI; calculated as weight in kg divided by height in m^2) of the patient was below average for a healthy woman (15.9 kg/m^2). This finding raised the differential diagnosis of malnutrition and malabsorption. Hence, the initial laboratory testing performed on the patient included a complete blood count, serum albumin assay, iron studies, assays of folate and B12 levels, and *Helicobacter pylori* antibody testing.

The initial laboratory results for the patient revealed decreased mean corpuscular hemoglobin concentration, increased RBC distribution width, and normal hemoglobin levels (**Table 1**). *H. pylori* antibody testing results were notable for an equivocal result of 1.05, so we started the patient on a regimen of daily omeprazole, which improved her early satiety. Her laboratory results showed a folate level consistent with insufficiency and included biochemical features of iron deficiency (**Table 1**). Her medical history did not reveal any fatigue or anemia that might have indicated folate deficiency. The patient has had normal balanced diet throughout and reported neither history of intake of antifolate medications nor alcoholism. Her serum vitamin B12, albumin, and homocysteine levels were normal. Her vitamin D levels were decreased, and she had osteopenia, as determined via bone densitometry testing. Based on the aforementioned information, we ordered a screening panel for celiac disease, the results of which revealed increased titers of immunoglobulin (Ig)A, IgA gliadin, IgG gliadin, IgA tissue transglutaminase, and IgG tissue transglutaminase. The results of repeat testing for IgG *H. pylori* titers were normal.

Although the patient did not have diabetes, she had subclinical hypothyroidism due to thyroiditis (positive antiperoxidase antibodies). (Type 1 diabetes mellitus and autoimmune thyroiditis can cluster with celiac disease.[12]) Stool studies revealed increased alpha-1-antitrypsin and fat, suggestive of chronic diarrhea, and fat malabsorption and decreased pancreatic elastase, suggestive of mild to moderate pancreatic enzyme deficiency. Duodenal biopsy confirmed a diagnosis of celiac disease with increased intraepithelial lymphocytes and severe villous blunting. The medical team treating the patient started her on a gluten-free diet (GFD) with 5 mg per day of folate supplementation. After 4 months, the patient reports significant symptomatic improvement, with mild improvement in her weight (she gained approximately 3 lbs in 3 months), iron, and vitamin D levels. However, she admitted that she did not totally comply with the GFD. At that point, her folate levels were within the reference range. The patient complies on the gluten free diet and has an improvement in her overall symptoms.

Discussion

Celiac disease, once considered a rare condition that predominated among individuals of European ancestry,[4] now has a worldwide distribution, with increasing incidence among persons of various ethnic groups and ages. The prevalence of celiac disease is nearly 1% in Western nations and has extended beyond that area to include populations in the Middle East, Asia, South America, and North Africa. This occurrence might be happening due to the globalization of the world market, in which developing nations that usually relied on gluten-free foods, such as rice and maize, are gradually including wheat-based foods into their diets.[5]

Only a proportion of celiac disease is clinically evident and considered to be a common and presumed cause of diarrheal illness. However, early diagnosis is desirable in all cases because a gluten-free diet prevents morbidity and reduces the incidence of GI malignant neoplasms and osteoporosis. The availability of serological tests for celiac disease allows the possibility for screening of high-risk populations; however, random screening is not a cost-effective option in healthy and/or asymptomatic individuals.[6]

Herein, we present the case of a 49-year-old female patient of Asian Indian descent with no significant GI symptoms but with folate and iron deficiency. Despite these 2 deficiencies, the patient did not have anemia. To develop megaloblastic anemia, it appears that one must have a plasma folate level of less than 3.0 ng per mL during a period of 3 to 6 months. Although the patient has mild iron deficiency without anemia, this finding can be a manifestation of celiac disease, a coexisting *H. pylori* infection, menstrual blood loss, or a diet enriched with phytates and phosphates that inhibits the absorption of nonheme iron. The moderate pancreatic enzyme deficiency of the patient also can be explained by her longstanding, untreated celiac disease. Pancreatic exocrine deficiency in populations such as Asian Indians can be explained by reduced cholecystokinin (CCK)

Table 1. Salient Laboratory Tests and Results for Our Patient, a 49-Year-Old Woman of Southeast Asian-Indian Descent

Test	Reference Range	At Time When Treatment Began	>4 Months After Treatment
Folate			
RBC folate	>112 ng/mL	<67	237
Serum folate	≥7.0 ng/mL	3.6	19.0
Hematology			
Leucocyte count	4.5-11.0 K/mm^3	7.1	8.2
RBC count	4.0-5.2 M/mm^3	4.53	4.3
Hemoglobin	12.0-16.0 g/dL	12.2	12.2
MCV	80-100 U/M^3	85.6	88.7
MCHC	32%-36%	31.5	31.9
RDW	0-14.7 U	21.4	16.1
Metabolic parameters			
Serum homocysteine	3.8-11 μmol/L	9.9	7.2
Serum albumin	3.4-4.8 g/dl	3.4	Test not performed
Vitamin B12	213-818 pg/ml	468	25.8
Vitamin D	30.0-100.0 ng/ml	25	25.8
Serum immunoglobulins			
IgA	81-426 mg/dL	1027	526
Gliadin, IgA	2,3,4,5: ELIA U/mL	>142	>142
Gliadin, IgG	<7 Negative	199	>302
Tissue transglutaminase, IgA	7-10 Equivocal	>128	>128
Tissue transglutaminase, IgG	>10 Positive	5	5
Serum iron studies			
Iron	42-135 μg/dL	28	44
Ferritin	10-291 ng/mL	5	7
Transferrin	192-382 mg/dL	202	261
TIBC	280-400 μg/dL	281	363
Iron % saturation	15%-50%	10.0	12.1
Stool studies			
Alpha-1-antitrypsin	0.50 mg/g		Increased
Fecal fat	201 μg/g	106	Test not performed
Pancreatic elastase	>1.13	Not performed	Test not performed
Miscellaneous chemistry			
Thyroid-stimulating hormone	0.35-3.30 IU/mL	4.06	6.28
Free T4	0.56-1.64 ng/dL	0.90	0.75

RBC, red blood cell; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; MMA, monomethylamine; NA, not applicable; IgA, immunoglobulin A; ELIA, enzyme labeled anti-isotype assay; IgG, immunoglobulin G; TIBC, total iron-binding capacity.

secretion from the diseased mucosa, resulting in inadequate postprandial stimulation of the pancreas.[7-8] Although the baseline homocysteine levels of the patient were normal, they fell with folate supplementation. This finding suggests a relative increase to the baseline laboratory values of the patient before her decreased folate status. The patient has admitted to having difficulty complying with a strict GFD, given that wheat products are staples of an Asian Indian diet; this information could explain the elevated antibody titers, as could the short duration of follow-up.

It has been suggested colloquially that even asymptomatic patients with isolated iron or folate deficiency must be referred directly for endoscopic duodenal biopsy; however, currently, many of these patients are lost to follow-up or are not referred at all for further investigations for celiac disease.[9] Previous studies[4,10] suggest that approximately 5% of patients with iron and/or folate deficiency with a positive results via serologic celiac-disease antibody testing had histologically confirmed celiac disease.[10] This value is 5 to 10 times greater than that which might be expected from random serological screening in the general population. Iron deficiency has been reported in as many as half of the newly diagnosed adult patients and folate deficiency in 35% to 49% and is, by itself, an indication for screening.[11,12]

In conclusion, if a patient, particularly a woman of Asian Indian descent who lives in a country in which the food

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supply is fortified with folate and who consumes a diet rich in legumes and vegetables, has a low folate level, further work-up for celiac disease and other causes is warranted, to allow early diagnosis and treatment. **LM**

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