CASE REPORT

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Celiac Disease as a Cause of Anemia and Brittle Diabetes in Type 1 Diabetes Mellitus

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Abstract

Untreated celiac disease (CD) leads to an increased risk for hypoglycemia and diabetic complications. However, the diagnosis of CD can be challenging and some extra-gastrointestinal tract manifestations could be a presenting symptom. We report a case of a 29-year-old Indian male with brittle T1DM whose underlying CD was discovered from a work-up for anemia. After an introduction of a gluten-free diet, he gained 5 kgs in two months, was responsive to oral iron supplement, and had stable glycemic control with much less hypoglycemia. Even though this disease is rare in Asian populations, the diagnosis of celiac disease should always be kept in mind when people with T1DM present with unexplained microcytic anemia and/or unexplained hypoglycemia.

Key words: Celiac disease, Type 1 diabetes, Brittle diabetes

INTRODUCTION

Celiac disease (CD) is a disorder of gluten-sensitive enteropathy that occurs in genetically susceptible individuals after dietary exposure to gluten.[1] The alcohol-soluble component of gluten called "*gliadin*" does not degrade in the intestinal lumen and causes inflammation in the small intestine. The prevalence rates of CD vary considerably by geographic location and genetic predisposition, with higher rates found in northern latitudes compared with southern latitudes.[2] Moreover, the frequency of those presenting with non-classic features which are commonly associated with malabsorption has increased. There is also a strong familial component to this disease with the prevalence of CD among first-degree relatives being up to 5 times than the general population.[3]

The association of CD and type 1 diabetes mellitus (T1DM) has been known for more than 40 years with prevalence varying from 1% to 8% (contrasted with only less than 1% in the general population). Both diseases have a common genetic basis in the major histocompatibility complex class II antigen DQ2 and DQ8 alleles together with shared non-human leucocyte antigen (HLA) loci.[4] Undiagnosed CD in T1DM patients lead to an increased risk for hypoglycemia and diabetic complications. The diagnosis of CD can be challenging and some extra-gastrointestinal tract manifestations could be a presenting symptom. We report a case of a 29-year-old Indian male with brittle T1DM whose underlying CD discovered was discovered from work-up of anemia. Elimination of gluten from the patient's diet allowed all symptoms including frequent hypoglycemia to improve substantially.

CASE

A 29-year-old Indian male with a 20-year history of T1DM presented with intermittent headache in the emergency room (ER). He reported fatigue, headaches, and 5-kilogram weight loss over a few months. He denied any gastrointestinal symptoms, palpitation, sweating, hematemesis, hematochezia, or hemorrhoids. The patient had moved from Rajasthan, a state in northern India to Bangkok, Thailand 2 years ago to work as a marketing technology developer. He was using a multiple daily insulin injection regimen with no other medications. His insulin regimen consisted of 12 units of insulin glargine at bedtime and regular insulin 10-12 units before meal. The last glycated hemoglobin (A1C) was 6.7% (50 mmol/mol) in India before moving to Thailand. No diabetic complications were reported.

Apart from T1DM, he had no pertinent past medical history. He had been breastfed for 1 year and had normal development. He had never smoked or used illicit drugs. After relocating to Thailand, he self-titrated insulin and did self-monitoring blood glucose (SMBG) 1-2 times per day but never attended regular follow-up in the hospital.

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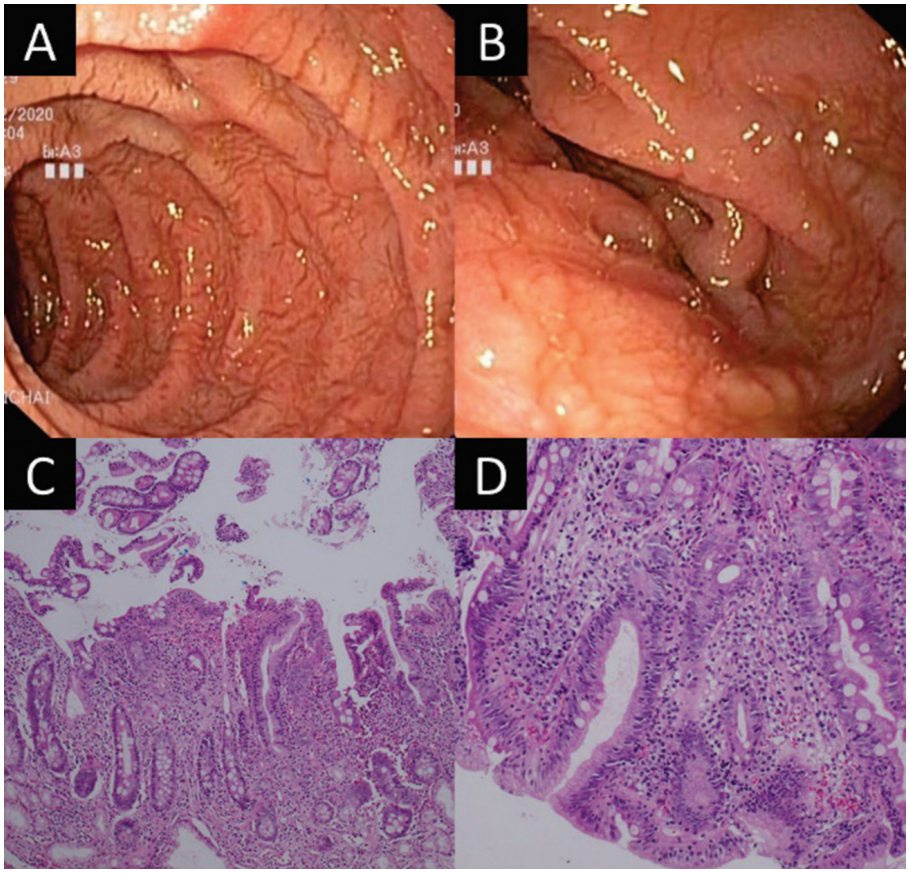

Figure 1. Endoscopic and pathologic findings in duodenum. **(A)** Endoscopy shows loss of mucosal folds. **(B)** Severe atrophic duodenitis. **(C)** Duodenal biopsy specimen showing subtotal villous atrophy and crypt hyperplasia (H&E, 100x). **(D)** Histologic changes in the duodenum characteristic of increased intraepithelial lymphocytosis and a chronic inflammatory infiltrate in the lamina propria (H&E, 200x).

The initial assessment in the ER showed a thin and pale Indian male without dysmorphic features. Upon physical examination, his height was 168 cm and weight was 45 kgs (BMI 16.1 kg/m^2). His blood pressure is 105/75 mm Hg. The rest of his examination findings were normal. He did not have subcutaneuous lipohypertrophy at insulin injection sites. Point-of-care testing (POCT) glucose 3 hours after lunch showed capillary glucose value at 54 mg/dL (3.0 mmol/L). Hypoglycemic unawareness was diagnosed and he had been given oral glucose to correct hypoglycemia. The initial laboratory data revealed A1C 5.7% (39 mmol/mol), hemoglobin 9.2 g/dL, MCV 65 fL, very low serum iron and ferritin levels. Oral iron supplement was given and further investigations were planned.

However, he was lost to follow-up for 9 months and came back with uncontrolled A1C at 8.0% (64 mmol/mol). At an outpatient follow-up, the patient described a 1-month history of feeling more tired and intermittent headache and increased frequency of nocturnal hypoglycemic episodes. He reported unstable glycemic values from 33-467 mg/dL (1.8-25.9 mmol/L) over a few months. He denied severe hypoglycemia requiring assistance. Additional history revealed that his mother in India had a recent diagnosis with celiac disease in the last month. The patient denied any abdominal pain, nausea, vomiting, or changes in weight or appetite. However, on further questioning, he noted occasionally irritable bowel syndrome-like symptoms and abdominal bloating in the past year. Therefore, celiac disease was suspected and further investigations were performed.

Tissue transglutaminase IgA antibody (IgA anti-tTgA) was positive at more than 200 RU/mL (reference range, <20 RU/mL). Other laboratory tests including thyroid function tests were normal. Upper gastrointestinal endoscopy was done and revealed severe atrophic duodenitis with scalloped duodenal folds. The results of histopathologic findings from random duodenal biopsies revealed subtotal villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes, shown in Figure 1. A diagnosis of celiac disease was confirmed and additional malabsorption-related problems were investigated.

Severe vitamin D deficiency (25-OH vitamin D 4.8 ng/mL, 12 nmol/L) with osteopenia (T-score -1.8 at lumbar spine) were found. Elevated serum aspartate transaminase (AST) at 68 U/L (normal <40 U/L), alanine transaminase (ALT) at 109 U/L (normal <41 U/L), and alkaline phosphatase 157 U/L (normal <129 U/L) were also noted. Abdominal ultrasonography was unremarkable except for diffuse heterogeneous echogenicity of liver parenchyma. Viral hepatitis and autoimmune hepatitis profiles revealed negative results. Liver biopsy showed mild non-specific change of hepatocytes without evidences of autoimmune hepatitis. Reactive hepatitis-associated CD was diagnosed.

The patient was referred to a dietitian for a strict gluten-free diet (GFD) and also was prescribed oral iron supplementation, calcium, vitamin D, and multivitamins. He was also advised to do SMBG frequently at least 3-6 times per day after initiation of GFD. After its introduction, the patient gained 5 kgs in 2 months and had stable glycemic control at 6.6% (49 mmol/mol) with much less hypoglycemia. His total insulin dose per day was reduced from 48 units per day to 40 units per day. Improvements of headaches and fatigue were also noted within the first month after the GFD initiation and completely relieved at 3 months. Laboratory follow-up revealed a hemoglobin of 15.7 g/dL and MCV of 83 fL at 3 months, then oral iron supplement was stopped.

The patient switched the approach of monitoring his daily glycemic control from SMBG to intermittently scanned continuous glucose monitoring (isCGM, FreeStyle Libre) at 3 months. As shown in Figure 2, the time-in-range (70–180 mg/dL, 3.9-10.0 mmol/L) was achieved at 69% and time spent in hypoglycemia (less than 70 mg/dL, 3.9 mmol/L) was at only 3%. His follow-up A1C varied from 5.9% to 7.3% (41 to 56 mmol/mol) during the period of 18 months after the confirmed diagnosis of celiac disease. The follow-up liver function tests were returned to normal values at 6 months. The follow-up IgA anti-tTgA at 6 months and 12 months revealed results at 54 RU/mL and less than 20 RU/mL respectively, confirming dietary adherence with GFD.

DISCUSSION

Our case highlights several important points about associated CD in patients with T1DM especially in extra-gastrointestinal tract manifestations. First, a high degree of clinical suspicion including awareness of geographic and ethnic data in expatriates is needed in evaluation of T1DM patients. The prevalence of CD from the northern part of India (Punjab, Haryana, Delhi, Rajasthan, Uttar Pradesh) where wheat rather than rice is the staple food is nearly the same as that reported from Western countries.[5] Recent data suggest that asymptomatic or non-classic presentations of CD are common in patients with T1DM and could affect unstable glycemic control from malabsorption problems.[6] Therefore, a low screening threshold for serologic testing is warranted in these patients.

Second, the presence of iron deficiency anemia in the absence of known etiologies should be screened for celiac disease in high-risk CD patients including first-degree relatives of CD patients, patients with T1DM, autoimmune thyroid disease, Down's syndrome, and Turner syndrome.[1]

Third, when celiac disease and T1DM are both diagnosed together, a referral to professional dietitians is required to ensure GFD adherence without substitute dietary options of high glycemic index food choices. The effect of GFD on the quality of life had been demonstrated to improve after initiation in T1DM patients with symptomatic CD.[4]

Brittle diabetes or unstable diabetes control should be thoroughly investigated for co-existing medical conditions.[7] Even though routine serologic screening test for CD in adult patients with T1DM yield no clinical benefits,[8] the possible co-existence of CD in T1DM patients must be kept in mind in unexplained hypoglycemia or other non-specific symptoms such as anemia, fatigue, paresthesia, infertility, amenorrhea, male impotence, and osteopenic bone disease. T1DM patients with undiagnosed CD have poor glycemic control and higher chance of diabetic complications. The mechanism of unexplained hypo- or hyperglycemia in T1DM patients with CD is believed to be due to disordered food absorption from immune-medicated enteropathy and inadequate food intake due to gastrointestinal symptoms.

The development of unstable blood glucose patterns tends to occur in the postprandial period due to food

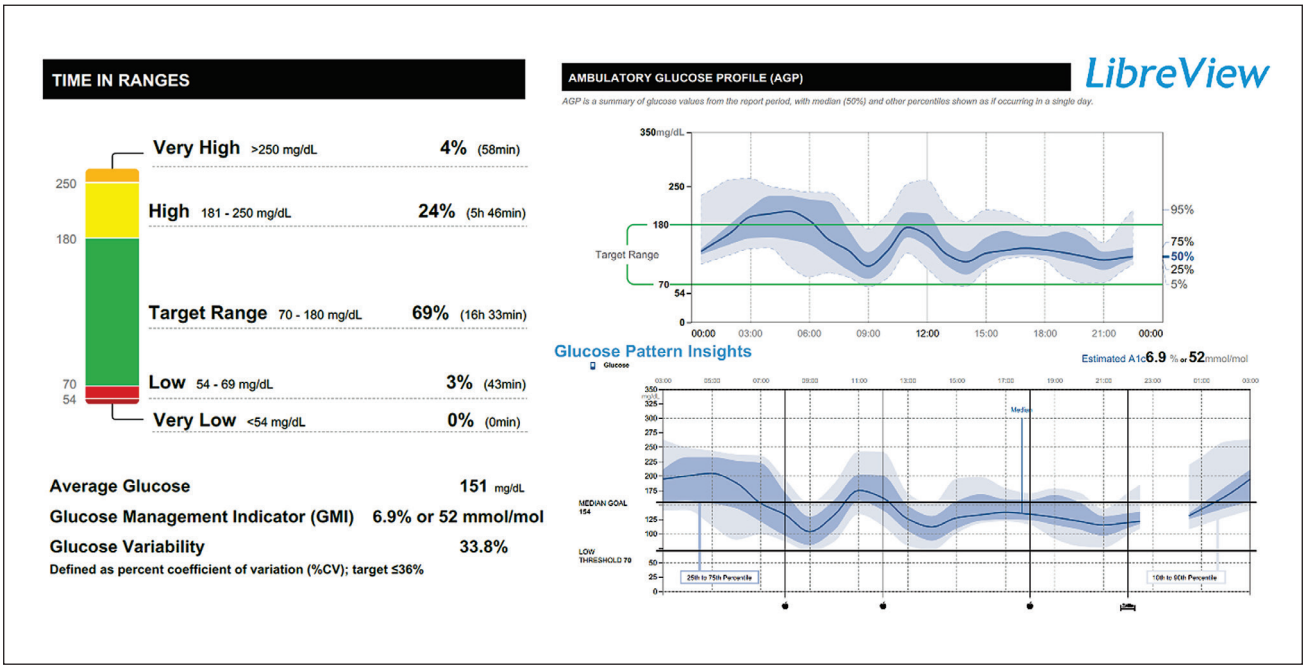

Figure 2. Intermittently scanned continuous glucose monitoring (isCGM) recorded through 14-day showed time-in-range (70–180 mg/dL) at 69% after a strict gluten-free diet for 3 months.

malabsorption.[4] Clinical manifestations of CD are determined by the severity and the extent of the intestinal lesions. Due to its protean clinical manifestations, it is an easy to miss diagnosis or misdiagnosis. Available evidence suggests that young age at onset of T1DM increases the risk of CD.[4] However, one needs to be aware that CD is not only a disease of children. The majority of cases were asymptomatic and identified only by screening tests. A high index of suspicion in a patient with a confounding presentation is required to diagnose CD. If diagnosed early, completely reversible complications from CD might be achieved with initiation of a GFD as shown in our present case.

Anemia is the most common hematological manifestation of CD due to impaired iron absorption in the upper part of the small intestine and could be the sole presenting symptom.[9] The suggestive feature of anemia-associated with CD in patients without obvious evidence of gastrointestinal bleeding is its refractoriness to oral iron supplement due to iron malabsorption. Up to 50% of CD patients could show positive fecal occult blood tests from villous atrophy in the small bowel. Moreover, untreated patients are at higher risk of developing a rare enteropathy-associated T-cell lymphoma.[1] Celiac screening should be considered in the diagnostic algorithm of high-risk patients with anemia.

The only current treatment for CD once discovered is a strict lifelong GFD. A strong commitment is warranted to eliminate any possible contaminated gluten in food and also over-the-counter medications. In patients with T1DM, the co-existence of CD could limit food choices and can be a burdensome in affected patients especially patients who do not prepare food in their homes. Carefully checking the food labels for ingredients in packaged food and encourage patients to join a peer support group for CD should be recommended in all newly diagnosed patients.

Periodic serologic testing for IgA anti-tTgA could allow for quantitative measurement of the severity of mucosal damage and monitoring dietary adherence in some patients who still have symptoms after treatment. Excessive weight gain as a consequence of fat ingestion, commonly present in GFD is also another challenge in CD patients.[10] Mindful eating and regular follow-up with professional dietitians or nutritionists is important to prevent this unintended consequence of GFD. It cannot be overemphasized that the management of these patients requires experience and expertise of a dedicated clinical team.

CONCLUSION

Our case highlights the importance of CD awareness in T1DM patients with unstable glycemic control due to erratic absorption of digested food and also in patients with iron deficiency anemia. The multifaceted clinical presentation of CD leads to several manifestations that physicians, other than gastroenterologists might encounter. Clinical vigilance is needed to promptly diagnose these patients and start lifelong treatment with GFD.

Ethical Considerations
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

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