

[CASE REPORT]

Celiac Disease Complicated by Rhabdomyolysis

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Abstract:

At 37 years old, a patient developed chronic watery diarrhea, generalized pain, severe hypokalemia and elevated creatine kinase levels. She was thought to have rhabdomyolysis due to hypokalemia from chronic diarrhea. No organic cause was found. Her symptoms subsided with potassium correction, but hypokalemia persisted; she visited our hospital at 44 years old. Endoscopy detected prominent atrophy of the intestinal villi. Histology indicated Marsh-Oberhuber type-3b disease. Anti-gliadin and anti-tissue transglutaminase IgA antibody tests were positive. She was diagnosed with celiac disease and started on a gluten-free diet, which improved her symptoms. This report is only the tenth of its kind worldwide.

Key words: celiac disease, rhabdomyolysis, hypokalemia

(Intern Med 60: 217-222, 2021)

(DOI: 10.2169/internalmedicine.5358-20)

Introduction

Celiac disease (CD) is an autoimmune intestinal disease that can occur in people with certain genes, including human leucocyte antigen (HLA)-DQ2 and HLA-DQ8. The symptoms of CD are triggered by the ingestion of gluten (1). Gluten is a major protein contained in wheat, barley and rye. It is incompletely digested by gastric and pancreatic juices. Following digestion, the gliadin 33-mer peptide, which is a large peptide, remains in the intestine. When the peptide enters the small intestine, an immune reaction that depends on the deamidation of gliadin molecules by tissue transglutaminase (TTG) is initiated (2). It has been found that deamidation enhances the immunogenicity of gliadin and facilitates the binding of gliadin to HLA-DQ2 or HLA-DQ8 molecules on antigen-presenting cells (3). As a result, those with HLA-DQ2 or HLA-DQ8 genes have a high risk of CD.

CD4+ T cells, which can be found in the lamina propria of the intestine, produce inflammatory cytokines, including interferon- γ , when they recognize deamidated gliadin peptides presented by HLA-DQ2 and DQ8. Furthermore, the cells cause the hyperplasia of the intestinal crypt and dam-

age villi as they activate cytotoxic factors such as metalloproteinase (4, 5). Moreover, gliadin peptides activate an innate immune response in the intestinal epithelium, which is characterized by increased interleukin 15 expression in epithelial cells and the activation of intraepithelial lymphocytes (IELs). This leads to the destruction of intestinal epithelial cells and the atrophy of villi.

Epidemiological studies have suggested that CD shows gender, geographical and ethnic differences. While the reasons underlying gender differences are unknown, it has been found that the morbidity rate of CD in women is two to three times higher than in men (6). The prevalence rate of CD varies among countries. For example, in the United States (US), the rate is 1% (7, 8). In Europe, the prevalence in Germany is 0.3%, which is lower than in other European nations, whereas Finland has the highest prevalence at 2.4% (9). The number of CD cases has been increasing in India in recent years. It has been found that the morbidity rate is particularly high in northern India. A study found that while there was no marked difference in the proportion of people who had HLA-DQ2 or HLA-DQ8 between northern India and other Indian regions, wheat consumption was high in the former, which may be related to the morbidity difference (10). As for ethnicity, it has been reported that in

Table 1. Laboratory Findings.

WBC	11,100 / μ L	γ -GTP	14 U/L
RBC	4.72×10^6 / μ L	Amy	94 U/L
Hb	15.0 g/dL	T-Bil	0.2 mg/dL
Ht	42.4 %	BUN	9 mg/dL
Plt	52.2×10^4 / μ L	Cr	0.6 mg/dL
CK	5,838 U/L	Glu	126 mg/dL
ALT	183 U/L	Na	142 mEq/L
AST	237 U/L	K	1.4 mEq/L
LDH	376 U/L	Cl	101 mEq/L
ALP	250 U/L	CRP	0.11 mg/dL
		Myoglobin	>5,000 ng/mL
1 month after GFD			
Anti-tissue transglutaminase antibodies (tTG)			
		tTG-IgA	5 U/L (≥ 4)
Anti-gliadin antibody (AGA)		AGA-IgA	38 U/L (> 20)
		AGA-IgG	10 U/L (> 20)

GFD: gluten free diet

the US, the prevalence in African Americans is lower than in Caucasians (11). In addition, the incidence rate in African Americans is low in Brazil (12).

CD is considered a rare disease in Japan. In a study of 2008 healthy Japanese individuals who attended a health checkup, 4 (0.19%) tested positive on a TTG test (13). These four individuals underwent a duodenal biopsy, and 1 (0.05%) received a definitive diagnosis of CD. The prevalence rate found in that study was thus far less than the rates found in Europe and the US.

As for HLA typing, the prevalence rates of HLA-DQ2 and DQ8 in Japan were 0.6% and 7.6%, while those in the US were 13.1% and 4.2%, respectively, suggesting that the low CD morbidity in Japan may partially be explained by a low HLA-DQ2 presence (14, 15).

The typical symptoms of CD include fatty stools, diarrhea and weight loss. Chronic diarrhea may cause hypokalemia as a complication. Although extremely rare, CD patients may develop intercurrent rhabdomyolysis with hypokalemia (16-24). We herein report an extremely rare case of rhabdomyolysis that occurred following hypokalemia due to chronic diarrhea.

Case Report

A 36-year-old woman presented at a local clinic with malaise and pain in the extremities and knees. However, no abnormalities were found on an examination. At 37 years old, the patient suffered from persistent watery diarrhea (4-5 times/day). One month later, she developed muscle pain mainly in the extremities, as well as high serum creatine kinase (CK) levels and liver dysfunction. The patient visited the emergency room (ER) of our hospital and was admitted as an emergency case. The results of blood tests performed during the visit showed a CK level of 5,838 U/L, a myoglobin level of >5,000 ng/mL and a potassium level of 1.4

mEq/L (Table 1). She was thus thought to have developed rhabdomyolysis, likely due to hypokalemia resulting from chronic diarrhea. A detailed evaluation of the chronic diarrhea did not detect any organic cause. The rhabdomyolysis and hypokalemia improved with infusion of potassium, and the patient was discharged.

The patient was hospitalized for similar symptoms at 43 years old and treated and discharged in the same way. Following the hospitalization, she received anti-diarrheal drugs and potassium supplements at a local clinic. Since the medications did not improve the hypokalemia and chronic diarrhea, the patient was referred to our hospital and presented to us again at 44 years old. The patient's history was significant for anemia at 36 years old. Her mother had Hashimoto's disease and interstitial pneumonia. The patient had no drug or food allergies.

Dilatation of the small intestine and colon as well as edema were observed on abdominal computed tomography, but there were no findings suggestive of gastrointestinal obstruction. Upper gastrointestinal endoscopy showed mucosal atrophy extending from the duodenal bulb to the third segment of the duodenum. Mosaic patterns, which can be associated with deep mucosal grooves (25) that are characteristic to CD, were also observed (Fig. 1). Atrophy of the villi was observed throughout the entire small intestine on capsule endoscopy (Fig. 2). Atrophy of the villi and infiltration of chronic inflammatory cells into the lamina propria were observed in Hematoxylin and Eosin-stained samples from a duodenal biopsy (Fig. 3). Immunohistochemically, the lymphocytes infiltrating the epithelium were CD3-positive T-lymphocytes. The IEL count was 70-80 per 100 enterocytes, and the degree of villi atrophy was moderate. The patient's condition was classified as Marsh-Oberhuber type 3b. The patient's history, symptoms and examination findings strongly suggested that she suffered from CD.

Following the commencement of a gluten-free diet

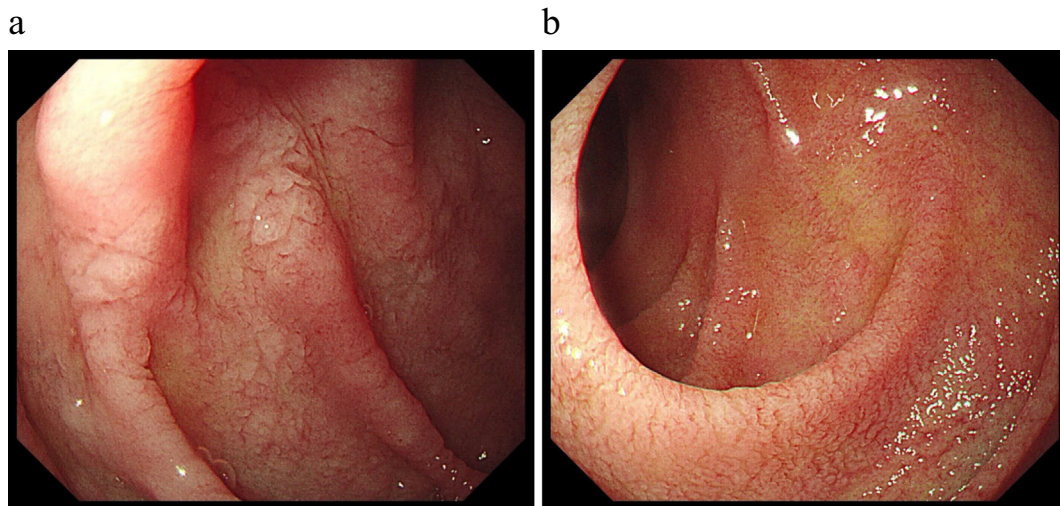


Figure 1. Upper gastrointestinal endoscopic images. a: The second segment showing mosaic patterns, which are characteristic of celiac disease; b: The third segment showing prominent atrophy with flattening of the villi.

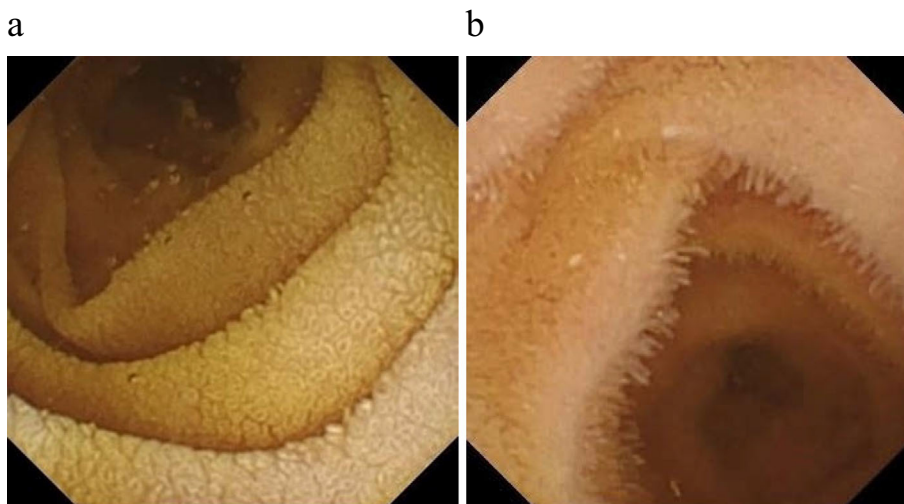


Figure 2. Small intestine capsule endoscopic images comparing the present case and a healthy individual. a: Small intestine, showing prominent atrophy of the villi. b: Normal small intestinal villi.

(GFD), the diarrhea and hypokalemia improved. A serological test performed a month after implementing the GFD was weakly positive for anti-gliadin IgA antibody and anti-tissue transglutaminase IgA antibody (Table 1). Therefore, the patient was finally diagnosed with CD, and the resulting hypokalemia due to chronic diarrhea was recognized as the cause of the recurrent rhabdomyolysis. HLA-typing of the patient subsequently revealed the presence of HLA-DQ4/6.

Discussion

CD results from the interaction between gluten and immune, genetic and environmental factors (6). CD is common in Caucasians, and carrying HLA-DQ2 or DQ8 is a significant genetic risk factor (6, 8). In fact, in a large European collaborative study, only 20 of 1,008 patients (2.0%) met the criteria for CD without carrying DQ2 or DQ8 (26). Two ad-

ditional studies in the US and Italy found the prevalence of DQ2/DQ8 negativity in CD patients to range from 0.16% to 0.9% (27, 28). Therefore, carrying HLA-DQ2/8 is such a strong genetic risk factor that developing CD in its absence is very rare, at least in Western countries. In contrast, CD is very rare in Japan, and only four patients, including the present patient, who underwent HLA typing were identified in the literature. Among these, one patient carried DQ8, but the other three did not exhibit DQ2/8 (13, 29, 30). Other factors assumed to contribute to the development of CD include viral infection, tissue damage and early termination of breastfeeding (31), all of which may play a prominent role in the development of CD in the Japanese population.

Rhabdomyolysis is a condition in which there is rapid breakdown and necrosis of skeletal muscle cells. In rhabdomyolysis, muscle cellular components, including myoglobin (Mb), are released into the blood, causing acute renal injury

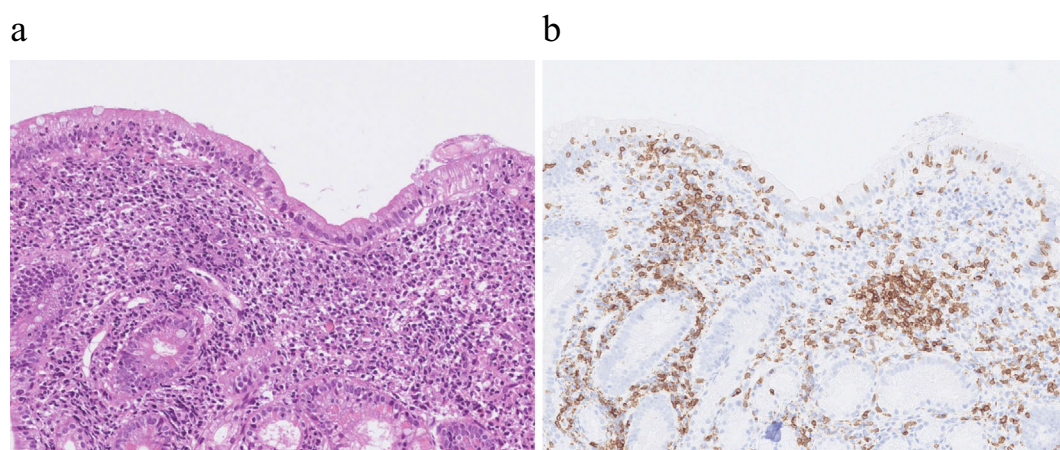


Figure 3. Pathological findings from the biopsy of the duodenum. **a:** Hematoxylin and Eosin staining: Atrophy of the villi and infiltration of inflammatory cells into the lamina propria were observed; intraepithelial infiltration of inflammatory cells, which is characteristic of celiac disease, was observed. **b:** Immunostaining with CD3 antibody: The intraepithelial infiltration of CD3-positive T-lymphocytes.

Table 2. Previous Case Reports on Celiac Disease with Rhabdomyolysis (including the Present Case).

Reference	Age	Sex	Clinical presentation	K(mEq/L)
(16)	75	Male	Weakness,osteomalacia	2.1
(17)	60	Male	Weakness,chronic diarrhea	Low ^a
(18)	12	Female	Fatigue,failure to thrive, chronic diarrhea	1.2
(19)	20	Female	Weakness,weight loss, dyspepsia	2
(20)	12	Female	Weakness,failure to thrive, vomitting,chronic diarrhea	1.7
(21)	22	Female	Weakness,fatigue,vomitting, chronic diarrhea,dermatitis herpetiformis	2.1
(22)	38	Male	Weakness,fatigue,weight loss, chronic diarrhea	1.8
(23)	31	Female	Fatigue,weight loss,chronic diarrhea, acute renal failure	1.8
(24)	3	Male	Weakness,fatigue, intermittent diarrhea, abdominal bloating	2.8
Present case 2018	44	Female	Chronic diarrhea, limb pain	1.4

^aNot specified by authors

and other sequelae. The causes of rhabdomyolysis can be divided into traumatic and non-traumatic. Non-traumatic causes, such as in the present case, include drugs, toxins, infection, ischemia and electrolyte and metabolic disorders (32).

Hypokalemia-induced rhabdomyolysis was first reported by Van Horn et al. in 1970 (33). The researchers observed a prominent elevation of myogenic enzymes in three cases of hypokalemic paralysis of the extremities. They also observed necrotizing myopathy on muscle biopsy. Various factors

have been reported as causes of hypokalemia, which gives rise to rhabdomyolysis. These include diuretics (34), excessive alcohol consumption (35), Chinese herbal medicines (e.g. *kanzo*) (36), glycyrrhizin formulations and primary aldosteronism (37).

The mechanism by which hypokalemia induces rhabdomyolysis is yet to be fully elucidated. However, it may be related to the role of potassium in blood flow modulation by skeletal muscle. It has been found that potassium ions released from skeletal muscle dilate the surrounding arterioles

and increase local blood flow. When potassium is depleted, blood flow decreases, causing relative ischemia. This may give rise to muscle spasms, ischemic necrosis and rhabdomyolysis (38). A study found that animal models that received a low-potassium diet and corticosteroids developed rhabdomyolysis (39).

We searched PubMed for cases of CD complicated by rhabdomyolysis using the following keywords: “celiac disease” and “rhabdomyolysis.” The search found only 10 cases, including the present case (Table 2). Hypokalemia was present in all 10 cases. To assess the relationship between CD and hypokalemia, a study examined 126 patients with CD who were transported to an ER with symptoms such as severe diarrhea (40). The study found that the mean serum potassium level in these patients was 2.4 ± 0.55 mEq/L (mean \pm standard deviation). As shown in Table 2, the median serum potassium level in the 10 cases of CD complicated by rhabdomyolysis was 1.9 mEq/L, suggesting that they had severe hypokalemia complicated by rhabdomyolysis. The gender breakdown of these 10 cases was 4 men and 6 women, indicating no particular difference. No obvious age trend was observed either; the ages of these cases ranged widely from 3 to 75 years old. Taking into account the previously report (40), the actual number of patients suffering from CD with severe hypokalemia of approximately 1.9 Eq/L is likely much higher than 10 in the real-world setting. However, what factors other than hypokalemia trigger the onset of rhabdomyolysis is unclear. To determine the mechanism of the onset of the condition, it is necessary to examine more cases in detail. It may also be necessary to conduct basic science experiments using animal models.

The authors state that they have no Conflict of Interest (COI).

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