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CASE REPORT

An unusual Chinese case of celiac disease presenting as hypocalcemia and low bone density

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Introduction

Celiac disease (CD) is an immune-mediated small intestinal enteropathy that is triggered by exposure to dietary gluten in genetically predisposed individuals [1]. The typical manifestations of CD are diarrhea, steatorrhea, and malabsorptive symptoms [2], and the main predisposing genes are HLA-DQ2 and HLA-DQ8 [3]. The estimated prevalence of CD in adults in the USA and Europe was 0.2 to 1% [4]. With differing prevalence to Caucasian populations, CD was thought to be rare in China. We report an unusual Chinese case of CD in an adult who presented with hypocalcemia and secondary hyperparathyroidism, without gastrointestinal manifestations.

Case report

A 40-year-old Chinese woman presented with a 1-year history of back pain and 4-month history of tetany and numbness in her fingers. She had no perioral anesthesia, joint pain, morning stiffness, or history of seizures. In the preceding 2 years, she reported 1–2 bowel movements per day and rarely had loose stools. No anorexia, nausea, vomiting, diarrhea, steatorrhea, hematochezia, or abdominal discomfort was reported. She lost approximately 1 kg in the 2-year period. Her sleep pattern, diet, and urination were normal. She had had an appendectomy 3 years prior for acute appendicitis. The patient was a housewife and did not smoke or consume alcohol. She denied taking any medications, including herbal preparations. The patient had not travelled recently. She had a regular menstrual cycle and her menarche was at 16 years of age. The patient had a daughter and a son who were both healthy. Her parents and two siblings were alive and well.

The patient had pale conjunctiva on physical examination. Her body height was 158 cm and weight was 56.2 kg. Chvostek's and Trousseau's signs were positive. She had no scoliosis, pigeon chest, rib tenderness, genu varum, or valgum. Examination of cardiovascular and respiratory systems and her abdomen was normal.

Laboratory evaluation revealed hypocalcemia; hypocalciuria; elevated serum alkaline phosphatase, parathyroid hormone (PTH), osteocalcin, β-carboxyterminal telopeptide of type I collagen (β-CTX), and procollagen type I N-terminal propeptide (PINP) levels; and decreased serum 25-hydroxyvitamin D (25(OH)D) level, as shown in Table 1. In addition, she had microcytic hypochromic anemia (Table 1). Serum ferritin level was low at 6.10 ng/mL (normal 10.00–291.00 ng/mL), while serum folic acid (5.59 pg/mL;

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Table 1 Results of laboratory evaluation and bone mass density (BMD) measurement

Laboratory evaluation	Results			Reference value
	Before therapy	1-month follow-up	3-year follow-up	
Serum calcium	1.80	2.15	2.22	2.15–2.55 mmol/L
Serum phosphate	1.01	1.37	1.13	0.80–1.45 mmol/L
Albumin	43	43	45	35–45 g/L
ALP	314	291	59	40–150 IU/L
25(OH)D	15.75	–	59.62	47.7–144.0 nmol/L
PTH	50.4	4.98	20.4	1.1–7.4 pg/mL
Osteocalcin	86.85	–	49.45	11–48 ng/mL
β-CTX	2.35	–	0.77	0.30–0.57 ng/mL
PINP	275.3	–	78.6	19–84 ng/mL
Hb	93	110	100	110–150 g/L
MCV	76	80	78	82.0–95.0 fL
Ferritin	6.10	–	5.44	10.00–291.00 ng/mL[a] 4.60–204.00 ng/mL[b]
Triglyceride	0.38	–	0.62	0.57–1.71 mmol/L
DEXA	Before therapy		3-year follow-up	
	BMD (g/m^2)	*T*-score, *z*-score	BMD (g/m^2)	*T*-score, *z*-score
L1–L4	0.702	− 3.4, − 3.4	0.934	− 1.5, − 1.6
Femur neck	0.591	− 2.8, − 2.8	0.815	− 1.0, − 0.8
Total hip	0.589	− 3.0, − 2.9	0.862	− 0.9, − 0.8

ALP alkaline phosphatase, *25(OH)D* 25-hydroxyvitamin D, *PTH* parathyroid hormone, *β-CTX* β-carboxyterminal telopeptide of type I collagen, *PINP* procollagen type I N-terminal propeptide, *Hb* hemoglobin, *MCV* mean corpuscular volume, *DEXA* dual-energy X-ray absorptiometry, *L1–L4* lumbar spines 1–4

[a] Reference range for the value of ferritin before therapy

[b] Reference range for the value of ferritin 3 years after therapy

"–" indicates data were not available

normal 5.31–24 pg/mL) and vitamin B_{12} levels (421.00 ng/mL; normal 211–911 ng/mL) were normal. Her coagulation, liver, and renal function were normal. Triglyceride level was low at 0.38 mmol/L (normal 0.57–1.71 mmol/L). Her thyroid, adrenal corticoid, and gonadal function were normal. Blood gas analysis results were normal and the pH value was 7.38.

Osteopenia, blurred bone trabecular markings, and a slightly decreased femoral neck stem angle were seen on radiographs of her lumbar spine and pelvis. The *z*-score of her bone mass density (BMD) was − 2.8 at the femoral neck and − 3.4 at the lumbar spine, measured using dual-energy X-ray absorptiometry (DEXA) (Table 1). Chest X-ray was normal. The liver, gallbladder, bile ducts, pancreatic head and neck, spleen, and kidney appeared normal on ultrasound. Gastroduodenoscopy with distal duodenal biopsy revealed increased intraepithelial lymphocytes, crypt hyperplasia, and partial villous atrophy (Fig. 1). Serology tests were positive for anti-tissue transglutaminase antibody (titer 92.4 U/mL).

The presentation of severe hypocalcemia and vitamin D deficiency was accompanied with iron deficiency and hypotriglyceridemia. This led to the likely diagnosis of malabsorption due to CD. The results from the upper small intestine mucosa histology and serological testing confirmed the diagnosis of CD. Based on the results of bone X-ray films and DEXA, the diagnosis of low bone density was made. The remarkably elevated serum PTH level was considered to be attributable to secondary hyperparathyroidism, due to a severely low serum calcium level. Therefore, a gluten-free diet (GFD), as well as intramuscular vitamin D (300,000 IU), calcitriol (0.25 μg bid), calcium carbonate (600 mg bid), and polysaccharide-iron complex medications, was prescribed. On follow-up in clinic 1 month later, the patient showed marked improvements. Her back pain and muscle spasms had improved. The results of laboratory evaluations are shown in Table 1. The follow-up results further confirmed the previous diagnosis. Four weeks after the initial follow-up, the patient had stopped taking all medications and had not adhered to a strict GFD. The next follow-up took place 3 years later. The patient was asymptomatic and the results of laboratory evaluations are shown in Table 1. BMD using DEXA was significantly improved (Table 1).

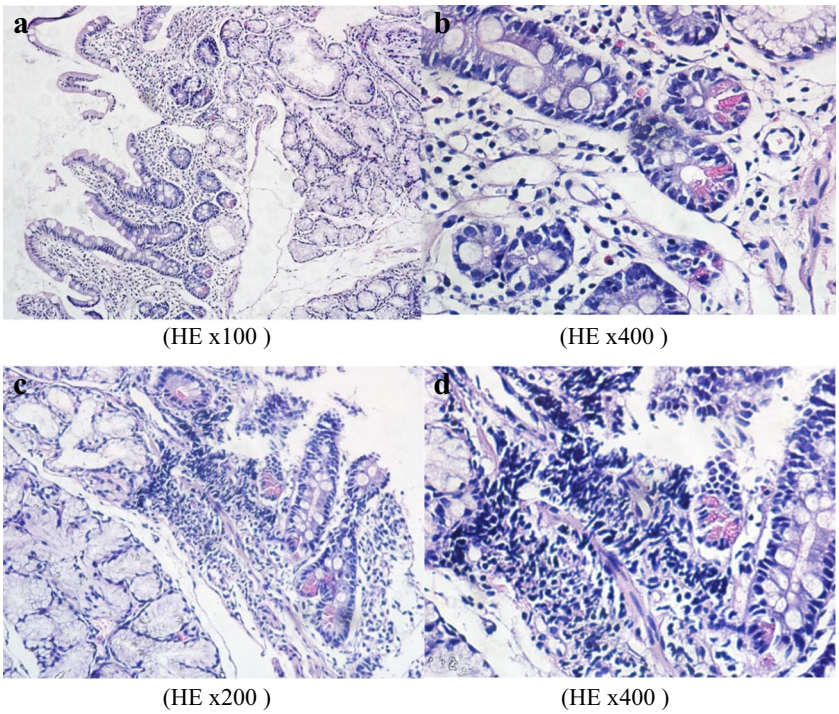

Fig. 1 Histologic examination of the distal duodenal mucosa (hematoxylin and eosin stain). **a** Partial villous atrophy, tunica mucosa thinning, and chronic inflammation. **b** Intestinal Paneth cell (with eosinophilic granules (pink) in the cytoplasm) hyperplasia. **c** Paneth cell hyperplasia in the epithelial glands, and the underlying collagenous band formation with lymphocyte infiltration in the superficial lamina propria. **d** Lymphocyte infiltration in the lamina propria and glandular epithelium, crypt hyperplasia, and Paneth cell hyperplasia

Discussion

CD was first described by Samuel Gee in 1887, and Dicke et al. [5] established a link between gluten and the pathogeny of CD in 1953. Classical CD manifests as gastrointestinal and malabsorptive symptoms. We report an unusual case of CD that presented as hypocalcemia, secondary hyperparathyroidism, and low bone density, without obvious gastrointestinal symptoms. There are rare case reports of hypocalcemia and low bone density as the presenting symptom of CD [6, 7], and this is the first similar Chinese case. Cases of CD without gastrointestinal and malabsorptive symptoms are defined as "non-classical CD" [2]. In addition to hypocalcemia and low bone density, other extraintestinal manifestations of CD, including anemia [8], ataxia [9], depression [10], short stature [11], and liver disease [12], have been described in the literature. Moreover, some cases of asymptomatic CD have been diagnosed through high-risk population screening or epidemiological survey [2]. In fact, the clinical manifestation of CD varies from asymptomatic to severely symptomatic, depending on the severity and extent of intestinal inflammation and villi atrophy. "Classical CD" is just the tip of the iceberg of all CD presentations.

Intestinal malabsorption and inflammation contributes to the pathophysiology of osteopenia in CD [13]. Calcium is absorbed in the small intestine through binding to calbindin, a vital protein in the calcium transport mechanism; thus, in CD patients, calbindin synthesis is damaged due to villi atrophy [14]. In addition, intraluminal unabsorbed fatty acids bind to calcium and further inhibit calcium absorption [13]. The above mechanisms, together with vitamin D deficiency, lead to hypocalcemia in CD. Hypocalcemia associated with vitamin D deficiency can impair bone mineralization, resulting in osteopenia. Moreover, hypocalcemia can stimulate PTH secretion, which may enhance the activity of the renal enzyme 1-α-hydroxylase and convert more 25-hydroxyvitamin D into 1,25-hydroxyvitamin D, to compensate for calcium malabsorption and bone mineralization impairment. Subsequently, there is an increase in bone turnover in order to maintain serum calcium level, resulting in net bone loss. Finally, serum proinflammatory cytokines, in particular TNF-α, IL-1, and IL-6, are elevated in CD and also play a role in the pathogenesis of osteopenia [13].

CD was believed to be rare in populations from the Asia-Pacific region and the number of reported CD cases is extremely low in China at present [15]; however, increasing evidence has revealed that the prevalence of CD in Chinese populations was underestimated. A study to determine the prevalence of CD in Chinese patients with chronic diarrhea predominant irritable bowel syndrome (IBS-D) revealed that CD was present in 1.01% of patients with IBS-D and in 0.28% of the control group [16]. A systemic review and meta-analysis analyzed data on frequencies of the predisposing genes HLA-DQ2 and HLA-DQ8, as well as the chance of being exposed to gluten in Chinese populations, and strongly suggested that the prevalence of CD might be much higher in China than that previously estimated [15]. With the development of

the economy and urbanization in China, a western diet is spreading widely, providing more gluten-containing foods (e.g., bread, cake). Meanwhile, the demand for gluten-containing convenience foods (e.g., instant noodles, biscuits) has rapidly increased. The change in diet may lead to an increase in gluten exposure by the Chinese population [15]; thus, genetically predisposed individuals are increasingly vulnerable to becoming overt CD patients. Furthermore, the incidence of autoimmune diseases has been increasing globally in recent years. These factors may be responsible for the increase in the prevalence of CD in China. However, the awareness of CD among physicians in China is low, and there are few professional dietitians who can provide appropriate counseling and supervision of patients in China. Therefore, measures should be taken to change this situation.

On 3-year follow-up, although the BMD was significantly improved, the biomarkers PTH, osteocalcin, and β-CTX were still elevated, which means the disease was only partly alleviated. This may be due to the patient's non-strict adherence to a GFD and reasons for this may be as follows. First of all, the patient lived in northern China, where wheat is part of the staple diet, so she ate foods made of wheat occasionally. Second, there is no label for gluten in processed foods in China, which leads to failure of the patient to identify gluten-containing foods. Third, the follow-up was irregular, resulting in failure of the patient to modify her diet. Unfortunately, the anti-tTG antibody and distal duodenal biopsy were not repeated on follow-up, and consequently we could not evaluate the extent to which the patient's condition had improved. This is a limitation of the case report.

In conclusion, "non-classical CD" can only manifest as hypocalcemia and osteopenia, and the prevalence of CD in Chinese populations may be underestimated.

Compliance with ethical standards

The study has been approved by the Ethics Committee of Tianjin Medical University General Hospital and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient.

Conflicts of interest None.

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