Case Reports

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(12) 1–6

DOI: 10.1177/03000605211061042
journals.sagepub.com/home/imr
SAGE

A fatal outcome in a patient with coeliac disease who suspended a strict gluten-free diet: a case report

Chong Lu, Xiao-Juan Zheng, Hong-Jun Hua and Qun-Ying Wang

Abstract

Coeliac disease (CD) is an autoimmune small bowel disease that occurs in susceptible individuals that develop an immunological reaction to gluten. A strict gluten-free diet (GFD) is the primary treatment for CD. This case report describes a patient with CD recurrence due to a discontinuation of a strict GFD by the patient. After recurrence, the patient developed fever and pancytopaenia, and quickly died of haemophagocytic lymphohistiocytosis (HLH). To the best of our knowledge, this is the first description of a case of CD associated with HLH due to discontinued GFD, which may contribute to improving the awareness of the importance of maintaining a strict GFD and having regular follow-up examinations.

Keywords

Coeliac disease, haemophagocytic lymphohistiocytosis, gluten-free diet, case report

Date received: 17 May 2021; accepted: 1 November 2021

Introduction

Coeliac disease (CD) is an autoimmune enteropathy caused by gluten intolerance, which is characterized by small intestinal mucosal lesions. A strict gluten-free diet (GFD) is considered the primary treatment for CD.[1] It has been reported that approximately 70% of patients with CD have symptomatic remission within 2 weeks after starting a GFD.[2] Herein, this case report presents a patient with recurrent CD due to a discontinuation of GFD. When the CD recurred, the patient developed fever and pancytopaenia, and quickly

Department of Gastroenterology, Jinhua Hospital of Zhejiang University, Jinhua, Zhejiang Province, China

Corresponding author:
Qun-Ying Wang, Department of Gastroenterology, Jinhua Hospital of Zhejiang University, 351 Mingyue Street Jinhua, Zhejiang Province 321000, China.
Email: wqy1177@126.com

died of haemophagocytic lymphohistiocytosis (HLH). HLH is a life-threatening haematological disorder, resulting from the proliferation, activation and dysfunction of macrophages.[3] It is clinically characterized by persistent fever, splenomegaly and pancytopenia.[4] HLH can be divided into two types: primary HLH and secondary HLH.[5] Primary HLH is a hereditary disease, while secondary HLH is associated with viral infections, autoimmune diseases and malignancies.[5] Secondary HLH often progresses rapidly, accompanied by dysfunctions of multiple organs within a few weeks.[5] This is, to the best of our knowledge, the first case of CD associated with HLH owing to suspended strict GFD treatment.

Case report

A 78-year-old man presented to the Emergency Room, Jinhua Hospital of Zhejiang University, Jinhua, Zhejiang Province, China due to diarrhoea and lower extremity oedema for 1 month in April 2016. He had also suffered from recurrent diarrhoea (2–6 loose stools per day) over the past 6 months. He had no history of abdominal pain, fever, nausea, vomiting, bloody stools or gastrointestinal infection. He underwent a gastroscope and colonoscopy 6 months previously and the results showed no obvious abnormalities.

When the patient was admitted to the Department of Gastroenterology, Jinhua Hospital of Zhejiang University, Jinhua, Zhejiang Province, China in April 2016, he presented with an anaemic appearance while his vital signs were stable (temperature 37.1°C; pulse rate 92 beats/min; blood pressure 113/71 mmHg) as detected by physical examinations. In addition, the bowel sound was active during abdominal examination and severe oedema was observed in both lower limbs. The results from general physical, cardiopulmonary and neurological examinations showed no significant abnormalities.

Laboratory tests showed pancytopaenia (white blood cell count 2.5×10^9/l, haemoglobin 72 g/l, platelet count 44×10^9/l), a low albumin level (albumin 22.2 g/l), hypokalaemia (serum potassium 3.06 mmol/l), elevated serum immunoglobulin (Ig) A antibodies (5.6 g/l), deficient levels of vitamin B12 and folic acid, and positive results for anti-tissue transglutaminase (anti-tTG) and anti-deamidated gliadin peptide (DGP) antibodies. The results from autoimmune tests were negative, including negative rheumatoid factor, and negative anti-nuclear, anti-dsDNA, anti-Sm, anti-Scl 70 and anti-cardiolipin antibodies. The results of coagulation function test, urinalysis and stool analysis were normal. The concentrations of serum complement, IgG, IgA, IgM and light chains (κ, λ) were in the normal ranges. The result from bone marrow puncture suggested megaloblastic anaemia. Abdominal computed tomography showed bowel wall thickening in some parts of the small intestine (Figure 1a, 1b). A capsule endoscopy was performed and the result showed nodular mucosa and atrophic villi in both the jejunum and ileum, consistent with a diagnosis of CD (Figure 2a, 2b). Gastroscopy suggested rough duodenal mucosa and atrophic villi. Gastric biopsies showed chronic gastritis with erosion. Duodenal mucosa samples revealed chronic inflammation, increased intraepithelial lymphocytes, flat intestinal mucosa with reduced villi and infiltration of interstitial inflammatory cells, which were also consistent with a diagnosis of CD (Figure 3a, 3b).

A strict GFD treatment was carried out on the patient after diagnosis with CD. After 4-weeks of GFD treatment, the patient exhibited improved clinical symptoms, with the number of diarrhoeal episodes decreasing to once or twice daily and relief of the oedema of the lower

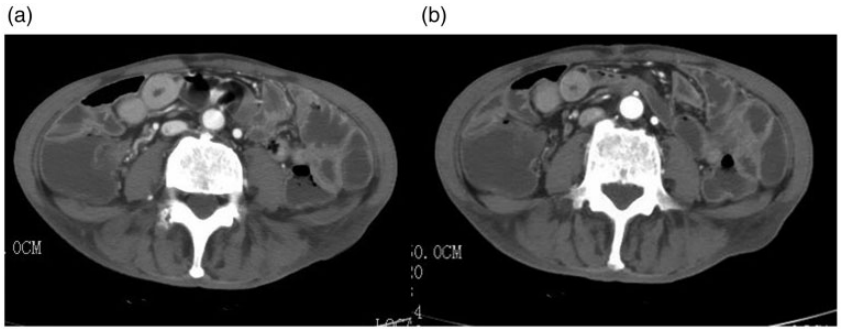

Figure 1. Abdominal plain computed tomography of a 78-year-old man that presented with diarrhoea and lower extremity oedema for 1 month shows localized thickening of the small intestinal wall (a, b).

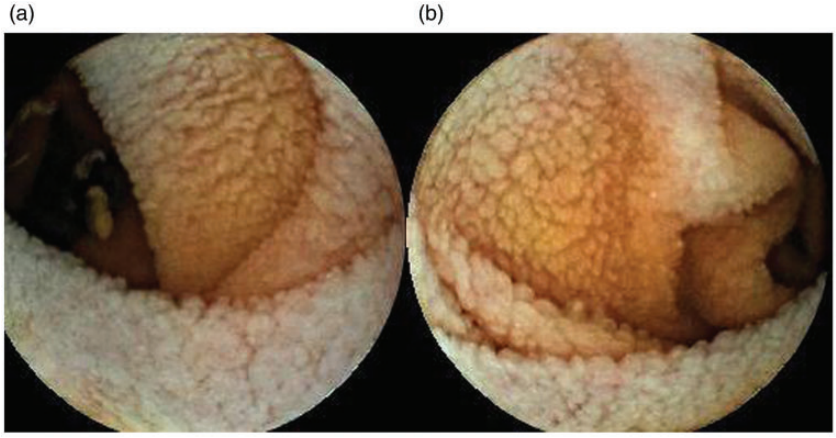

Figure 2. Capsule endoscopy of a 78-year-old man that presented with diarrhoea and lower extremity oedema for 1 month shows nodular mucosa and atrophic villi in both the jejunum (a) and ileum (b).

limbs. During a 2-year follow-up, the patient reported no significant discomfort. However, he thought he had completely recovered from CD and suspended the GFD on his own. Unfortunately, after suspension for 6 months, he experienced recurrent CD, developing fever, fatigue, diarrhoea and lower extremity oedema. The routine blood test showed that pancytopaenia had recurred (white blood cell count 0.4×10^9/l , haemoglobin 77 g/l, platelet count 22×10^9/l). Abdominal ultrasonography indicated that the spleen was enlarged. Additional serum biochemical tests showed hyperferritinaemia (1650 ng/ml, normal range 22–322 ng/ml) and hypofibrinogenaemia (1.5 g/l, normal range 2.38–4.98 g/l). Bone marrow puncture revealed that the mononuclear macrophage system was obviously active with the proportion of macrophages dramatically increasing, indicative of haemophagocytosis. The diagnosis of HLH was made and he was suggested to start chemotherapy to prolong survival. However, the patient refused further treatments and died 1 month later. This report conforms to the CARE guidelines.[6]

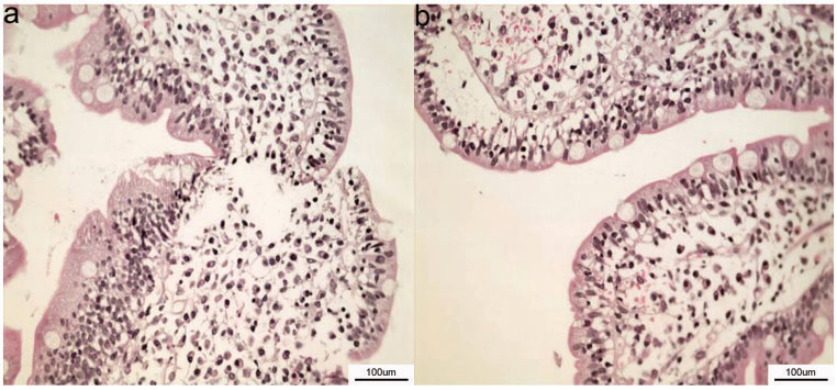

Figure 3. Histopathology confirmed the diagnosis of coeliac disease in a 78-year-old man that presented with diarrhoea and lower extremity oedema for 1 month. It showed chronic inflammation, increased intraepithelial lymphocytes, flat intestinal mucosa with reduced villi and infiltration of interstitial inflammatory cells (a, b). Scale bar 100 μm. The colour version of this figure is available at: http://imr.sagepub.com.

Discussion

Coeliac disease is a small bowel disease associated with autoimmune immunity, generally occurring in genetically-susceptible individuals that develop an immune reaction to gluten.[7] Numerous studies have confirmed that the cause of the disease is likely due to the interaction between genetics, immunity and dietary gluten; and gluten may be the causative agent of the disease.[1,8] New guidelines recommend that intestinal mucosal biopsy pathology forms the central basis for the diagnosis of CD.[7] Characteristics of small bowel biopsy include partial or complete atrophy of the villi, crypt hyperplasia, intraepithelial lymphocytes and plasma cell infiltration.[7,8] The positivity of serological tests (anti-tTG antibodies, anti-endomysium antibodies and DGP antibodies) are also beneficial for the diagnosis of CD.[7,8]

Haemophagocytic lymphohistiocytosis is a severe hyperinflammatory condition.[4] In 2004, the International Organizational Cell Association established the standards for its diagnosis.[9] If a patient fulfils five of the following eight criteria they are diagnosed with HLH: (i) fever; (ii) splenomegaly; (iii) cytopaenias affecting at least two of three lineages in the peripheral blood; (iv) hypertriglyceridaemia and/or hypofibrinogenaemia; (v) haemophagocytosis in the bone marrow, spleen or lymph nodes; (vi) low or absent natural killer cell activity; (vii) hyperferritinaemia; (viii) high levels of soluble CD25.[9] This current case fulfilled six of the eight diagnostic criteria (numbers 1, 2, 3, 4, 5 and 7) and was diagnosed with HLH according to the diagnostic criteria of the International Organizational Cell Association.[9]

The clinical symptoms such as splenomegaly and pancytopaenia can also occur in patients with other diseases including infection, lymphoma and lupus enteritis. Differential diagnosis is necessary for clinical decision-making in HLH. To differentiate with infection, an anti-infection treatment was administered to the current patient, but no significant positive effect was observed. To differentiate with lupus enteritis, autoimmune tests were undertaken on this patient. The results showed that rheumatoid factor, and anti-nuclear, anti-dsDNA, anti-Sm, anti-Scl 70, and anti-cardiolipin antibodies were all negative. The concentrations of serum complement,

IgG, IgA, IgM and light chains (κ, λ) were in the normal ranges. The results of the coagulation function test, urinalysis and stool analysis were normal. The patient did not demonstrate any enlarged lymph nodes, although lymph node biopsy was not undertaken for this patient because he refused to have any further examinations or treatment after being diagnosed with HLH. Thus, the evidence for the diagnosis of lymphoma was insufficient.

There has been one previous case of refractory CD associated with secondary HLH.[10] In that case, the patient was eventually diagnosed with enteropathy-associated T-cell lymphoma (EATL) and died on the day of the diagnosis.[10] EATL is a rare non-Hodgkin's T-cell lymphoma that originates in the intestinal epithelial T lymphocytes and is often associated with a history of CD.[11,12] It usually occurs in the jejunum or ileum, but can also occur in any part of the gastrointestinal tract.[11] HLH can be an uncommon and usually fatal complication of EATL.[13] It has been reported that six patients with EATL-related haemophagocytic syndrome died within 3 months after the appearance of haemophagocytic syndrome.[14]

In this current case, the patient's condition rapidly deteriorated into HLH after the patient discontinued the GFD. There have been no published case reports of CD associated with HLH in patients that discontinued GFD. Although GFD is effective in alleviating the typical symptoms of CD, the high price of gluten-free foods, potential gluten exposure, social pressures and even the presence of gluten in trace amounts in medications can be impediments to strict adherence.[1] The current patient suspended GFD after his symptoms disappeared. Unfortunately, CD quickly recurred and the patient refused treatment for HLH, probably because of the poor prognosis of HLH. In addition, the patient did not come to the hospital immediately after the occurrence of symptoms, making the diagnosis and treatment relatively late. These responses may account for the death of the patient.

In conclusion, this current case serves to remind gastroenterologists to regularly follow-up and urge their patients with CD to maintain a strict GFD. We recommend that patient education provided by clinicians should be greatly improved to enhance the patients' understanding of CD and GFD, which should improve their compliance with a GFD and promote regular follow-up. The role of nurses should also be emphasized to improve the patients' awareness of the importance of a strict GFD for CD treatment. Treatment regimens should be adjusted in a timely manner if the patient with CD cannot endure or continue the GFD in the long-term. Meanwhile, the risks of HLH and EATL in patients with CD should be evaluated as early as possible in order to improve the prognosis of patients.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and publication of this article: This work was supported by a grant from Jinhua Science and Technology Bureau (Grant ID: 2018-4-01).

ORCID iD

Chong Lu https://orcid.org/0000-0002-0865-5023

References

1. Lebwohl B, Sanders DS and Green PHR. Coeliac disease. *Lancet* 2018; 391: 70–81.
2. Hussain N, Hussain F, Chatterjee T, et al. An unexpected deterrent in diagnosing refractory celiac disease and enteropathy-associated T-cell lymphoma: a gluten-free

diet. *J Community Hosp Intern Med Perspect* 2018; 8: 233–236.
3. Esteban YM, de Jong JLO and Tesher MS. An Overview of Hemophagocytic Lymphohistiocytosis. *Pediatr Ann* 2017; 46: e309–e313.
4. Skinner J, Yankey B and Shelton BK. Hemophagocytic Lymphohistiocytosis. *AACN Adv Crit Care* 2019; 30: 151–164.
5. Al-Samkari H and Berliner N. Hemophagocytic Lymphohistiocytosis. *Annu Rev Pathol* 2018; 13: 27–49.
6. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. *Headache* 2013; 53: 1541–1547.
7. Al-Toma A, Volta U, Auricchio R, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol J* 2019; 7: 583–613.
8. Caio G, Volta U, Sapone A, et al. Celiac disease: a comprehensive current review. *BMC Med* 2019; 17: 142.
9. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; 48: 124–131.
10. Lu L, Ning S, Kassam Z, et al. Hemophagocytic Lymphohistiocytic Syndrome and Enteropathy-Associated T-cell Lymphoma in a Patient with Refractory Celiac Disease. *ACG Case Rep J* 2014; 1: 140–142.
11. Zettl A, deLeeuw R, Haralambieva E, et al. Enteropathy-type T-cell lymphoma. *Am J Clin Pathol* 2007; 127: 701–706.
12. Catassi C, Bearzi I and Holmes GK. Association of celiac disease and intestinal lymphomas and other cancers. *Gastroenterology* 2005; 128: S79–S86.
13. Varghese D, Haseer Koya H, Cherian SV, et al. Hemophagocytic lymphohistiocytosis: an uncommon presentation of enteropathy-associated T-cell lymphoma. *J Clin Oncol* 2013; 31: e226–e230.
14. Amiot A, Allez M, Treton X, et al. High frequency of fatal haemophagocytic lymphohistiocytosis syndrome in enteropathy-associated T cell lymphoma. *Dig Liver Dis* 2012; 44: 343–349.