



## Case report

## Celiac disease presenting as fever of unknown origin in the adult: The role of undiagnosed celiac disease in systemic atherosclerosis

*Gabriele Cioni*

*Department of Internal Medicine, Department of Experimental and Clinical Medicine, Careggi Hospital, University of Florence, Italy*

## ARTICLE INFO

## Article history

Received 28 April 2017

Accepted 4 September 2017

Available online 20 April 2018

## Keywords

Hyponatremia

Hepatic encephalopathy

Liver cirrhosis

## Doi

10.29089/2017.17.00034

## User license

This work is licensed under a  
Creative Commons Attribution –  
NonCommercial – NoDerivatives  
4.0 International License.



## ABSTRACT

**Introduction:** Celiac disease is an inflammatory disorder affecting subjects at any age and presenting with a broad spectrum of symptoms. In several cases, extra-intestinal symptoms are the only clinical manifestations or occur in conjunction with gastrointestinal symptoms.

**Aim:** We present the case of a 47-year-old male admitted to our Internal Medicine Department, after a further episode of fever with chill, associated with headache and malaise.

**Case study:** He had suffered from episodes of fever for about 20 years. At physical examination, gastrointestinal symptoms such as nausea, emesis, diarrheal and constipation, were absent.

**Results:** Investigations were negative for malignancy, haematological disorders, autoimmune diseases, and inflammatory bowel disease; serological and culture tests were negative for common infectious diseases and parasitosis. Inflammatory markers were elevated (erythrocyte sedimentation rate 48 mm/h, C-reactive protein 185 mg/L), with the exception of normal procalcitonin levels. Colonoscopy demonstrated villous blunting, with biopsies consistent with a diffuse chronic inflammation in the lamina propria and significant intraepithelial lymphocytosis (MARSH II). Further investigations showed an advanced atherosclerotic peripheral disease, despite the low cardiovascular risk.

**Discussion:** In celiac disease, the activation of gluten specific T cells in the gastrointestinal mucosa induces the activation of a pro-inflammatory pattern, which could contribute to the fever. The systemic inflammatory activation found in celiac disease was associated to a chronic vascular damage, both consisting in an increased arterial stiffness and intima-media-thickness.

**Conclusions:** The delay in diagnosis of celiac disease could be associated to several complications, such as atherosclerotic progression.

## 1. INTRODUCTION

Celiac disease is a lifelong, chronic, immune-mediated, inflammatory disorder affecting subjects at any age and presenting with a broad spectrum of symptoms; in several cases, extra-intestinal symptoms are the only clinical manifestations or occur in conjunction with gastrointestinal symptoms.<sup>1</sup> Cooney et al.<sup>2</sup> reported the first published case of celiac disease presenting as fever of unknown origin. Authors exposed the case of a 16-year-old female, presenting with one month of intermittent fever, a 5 kg weight loss, but without gastrointestinal disorders. Similarly, Leonardi et al.<sup>3</sup> described the case of 3-year-old child with silent celiac disease presenting with recurrent febrile infections and moderate neutropenia, normalized after the onset of a gluten free diet. The delay in the diagnosis of celiac disease can be associated with many complications. In particular, several observational studies have showed a small absolute increase in overall mortality in patients with undiagnosed celiac disease in comparison to the general population.<sup>4,5</sup> Moreover, population-based studies showed an association between celiac disease and cancer risk, with particular reference to non-Hodgkin's lymphoma.<sup>6</sup> In a previous report, authors described the case of a 13-year-old female from the Middle East with an 8-year history of severe rickets causing multiple bone deformities, after malabsorption for many years.<sup>7</sup> Previous studies investigated the association between cardiovascular profile and celiac disease in adults, showing an increased risk due to chronic inflammation.<sup>8,9</sup>

## 2. AIM

A 47-year-old male was admitted to the Internal Medicine Department of our hospital, after a further episode of fever with chill, associated with headache and malaise, which occurred two days before. We described the diagnostic workup and discussed the association between the peripheral vascular atherosclerosis and the delay in the diagnosis of celiac disease.

## 3. CASE STUDY

According to his medical history, the patient had suffered from episodes of fever for about 20 years, occasionally taking ibuprofen with benefit. Fever appeared not cyclical, with long periods between one episode and the next one, in which the patient reported complete well-being. From clinical records of previous hospitalizations, investigations were negative for malignancy, haematological disorders, autoimmune diseases, and inflammatory bowel disease. Serological and culture tests were negative for common infectious diseases and parasitosis. In particular, a previous celiac screen was negative. He was not diabetic, dyslipidemic, hypertensive, overweight or smoker. As collateral findings, he presented a mild atherosclerosis at common carotid arteries (intima media thickness over 2.0 mm), inconsistent with

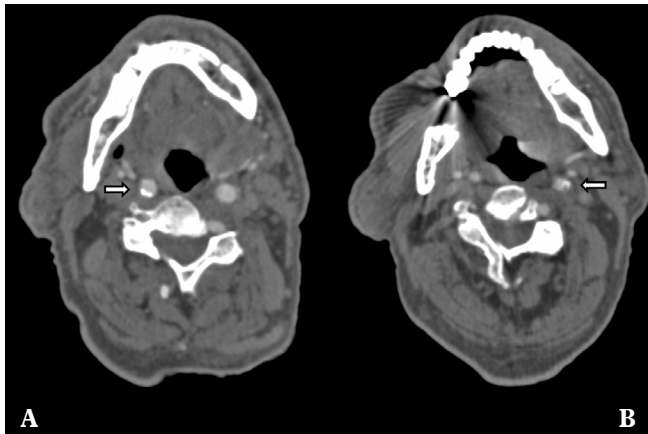
the low cardiovascular profile of our patient. He had no sick contacts and he had gone to Peru for work reasons about 5 years ago. His family history was negative for autoimmune diseases; his father was hypertensive. The patient currently was on no medications. He reported to assume a mostly vegetarian diet, and he never had gastrointestinal disorders or sudden weight loss in recent years.

On physical examination, sore throat, abdominal and chest pain, joint pain and other signs compatible with acute or chronic inflammation were absent. Gastrointestinal symptoms such as nausea, emesis, diarrheal and constipation, were absent. He appeared well, and his body mass index was 23.4 kg/m<sup>2</sup>. Apparently there were no signs of anaemia. His liver was 4 cm below the costal margin, and her spleen was palpable for 2 cm.

## 4. RESULTS

### 4.1. Biochemical parameters and instrumental exams

Complete blood cells count showed a mild reduction in haemoglobin level (12.7 g/dL), with normal volume of red cells; other cell lines on immunophenotype assay were within normal limits. Throat, blood and urine cultures were negative. We excluded viral, bacterial and parasitic infections: in particular, serological tests for human immunodeficiency virus-type 1 and 2, hepatitis B and C virus, Epstein-Barr virus, cytomegalovirus, were negative. Inflammatory markers were elevated (erythrocyte sedimentation rate 48 mm/hr, C-reactive protein 185 mg/L), with the exception of normal procalcitonin levels. Panel for autoimmune disease was negative. Thyroid function tests showed no alterations. Plasma levels of folic acid and B12 vitamin were significantly lower the minimum normal range (1.7 ng/mL and more than 60 pg/mL, respectively); serum ferritin level was within normal range. Cranial and thoracic CT scans were negative; abdominal CT scan demonstrated only a mild splenomegaly; abdominal ultrasound showed only a mild non-alcoholic fatty liver disease. In the suspicion of endocarditis, we prescribed transthoracic and transoesophageal echocardiography, showing normal findings. In order to exclude inflammatory bowel disease, the patient underwent upper gastrointestinal endoscopy, showing only a not specific gastric inflammation with biopsies consistent with a normal pattern, and colonoscopy demonstrating villous blunting, with biopsies consistent with a diffuse chronic inflammation in the lamina propria and significant intraepithelial lymphocytosis (MARSH II). He was started on a gluten-free diet and after a month from the discharge he was afebrile; inflammatory markers were significantly lower and haemoglobin levels were mildly increased. After discharge, the patients underwent further investigations in order to characterize the atherosclerotic involvement. Homocysteine and lipoprotein (a) were within normal values. We performed a vascular ultrasound assessment by a MyLab 70 XVision Esaote Machine equipped of a 7.5 MHz linear and a 3.75 MHz convex transducers machine (Esaote



**Figure 1. Computed tomography angiography of intracranial arteries: (A) a calcific plaque of right common carotid; (B) several calcific plaques of left internal carotid.**

Medical Systems, Rome, Italy). The system used a dedicated software (RF-data technology involving RF Quality Intima-media Thickness and RF Quality Arterial Stiffness; Esaote Medical Systems) in order to provide a standard assessment of intima media thickness and pulsewave velocity at common carotid and femoral arteries. Examinations demonstrated the presence of an extensive atherosclerotic involvement, associated to increased arterial stiffness at both carotids and femoral arteries. Thoracic and abdominal aorta were within normal limits. For this reason, we performed a CT angiography of intracranial arteries (Figure 1) and lower limbs, which showed a widespread atherosclerosis but without critical stenosis in the examined sites.

## 5. DISCUSSION

In our case, the patient was a 47-year-old man, having a positive history of recurrent fever and who presented a previous negative celiac disease screening. Fever is a key element of the inflammatory response, involving production and release of cytokines with endogenous pyrogenic activity.<sup>10</sup> In celiac disease, the activation of gluten specific T cells in the gastrointestinal mucosa induces the activation of a pro-inflammatory pattern, which could contribute to the fever; a such activated inflammatory response, was elsewhere associated to the epithelial damage at the basis of many common intestinal manifestations of the disease.<sup>11</sup> In a recent work, the systemic inflammatory activation found in celiac disease was associated to a chronic vascular damage, both consisting in an increased arterial stiffness<sup>12</sup> and intima-media-thickness;<sup>13</sup> our patient presented an atherosclerotic wall of common carotids and femoral arteries and a mild non alcoholic fatty liver disease, which is a well-established cardiovascular marker,<sup>14</sup> also associated to celiac disease.<sup>15</sup> In this case, because it was possible to recognize celiac disease only after many years, this delay may have contributed to increase the vascular damage and the global cardiovascular

risk, regardless of the presence of traditional cardiovascular risk factors. It is also known that autoimmune diseases are statistically associated with an increased risk of cardiovascular diseases, which are the leading cause of premature death in this patient population.<sup>16</sup> Therefore, to reduce diagnostic latency and to prevent clinical complications, directly<sup>17</sup> and indirectly<sup>18</sup> linked to celiac disease, it is mandatory to consider this disorder in the differential diagnosis of fever of unknown origin. Indeed, an early consideration of a gluten free diet may decrease the severe complications related to the disease and worsened with delaying the onset of therapy.<sup>19</sup>

## 6. CONCLUSIONS

In celiac disease, the activation of gluten specific T cells in the gastrointestinal mucosa induces the activation of a pro-inflammatory pattern, which could contribute to the fever. The delay in diagnosis of celiac disease could be associated to several complications; in this particular case, it may have led to atherosclerotic progression in different vascular districts. Therefore, it is mandatory to consider this disorder in the differential diagnosis of fever of unknown origin.

## Conflict of interest

None declared

## References

- 1 Leffler DA, Green PH, Fasano A. Extraintestinal manifestations of coeliac disease. *Nat Rev Gastroenterol Hepatol*. 2015;12(10):561–571. <https://doi.org/10.1038/nrgastro.2015.131>.
- 2 Cooney MJ, El-Matary W. Celiac disease presenting as fever of unknown origin. *Case Rep Gastrointest Med*. 2013;2013:676327. <https://doi.org/10.1155/2013/676327>.
- 3 Leonardi S, Vitaliti G, La Rosa M. Recurrent febrile infections and neutropenia in a child with silent celiac disease. *Clin Pediatr (Phila)*. 2010;49(2):146–149. <https://doi.org/10.1177/0009922809344426>.
- 4 Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology*. 2009;137(1):88–93. <https://doi.org/10.1053/j.gastro.2009.03.059>.
- 5 Ludvigsson JF, Montgomery SM, Ekbom A, Brandt L, Granath F. Small-intestinal histopathology and mortality risk in celiac disease. *JAMA*. 2009;302(11):1171–1178. <https://doi.org/10.1001/jama.2009.1320>.
- 6 Card TR, West J, Holmes GK. Risk of malignancy in diagnosed coeliac disease: a 24-year prospective, population-based, cohort study. *Aliment Pharmacol Ther*. 2004; 20(7):769–775. <https://doi.org/10.1111/j.1365-2036.2004.02177.x>.
- 7 Al-Sharafi BA, Al-Imad SA, Shamsair AM, Al-Faqeeh DH. Severe rickets in a young girl caused by celiac disease: the tragedy of delayed diagnosis: a case report. *BMC Res Notes*. 2014;7:701. <https://doi.org/10.1186/1756-0500-7-701>.

- 8 Viljamaa M, Kaukinen K, Pukkala E, Hervonen K, Reunala T, Collin P. Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. *Dig Liver Dis.* 2006; 38(6):374–380. <https://doi.org/10.1016/j.dld.2006.03.002>.
- 9 Wei L, Spiers E, Reynolds N, Walsh S, Fahey T, MacDonald TM. The association between coeliac disease and cardiovascular disease. *Aliment Pharmacol Ther.* 2008;27(6):514–519. <https://doi.org/10.1111/j.1365-2036.2007.03594.x>.
- 10 Dinarello CA. Cytokines as endogenous pyrogens. *J Infect Dis.* 1999;179 (Suppl 2):S294–S304. <https://doi.org/10.1086/513856>.
- 11 Rallabhandi P. Gluten and celiac disease – an immunologic perspective. *J AOAC Int.* 2012;95(2):349–355. [https://doi.org/10.5740/jaoacint.SGE\\_Rallabhandi](https://doi.org/10.5740/jaoacint.SGE_Rallabhandi).
- 12 Korkmaz H, Sozen M, Kebapcilar L. Increased arterial stiffness and its relationship with inflammation, insulin, and insulin resistance in celiac disease. *Eur J Gastroenterol Hepatol.* 2015;27(10):1193–1199. <https://doi.org/10.1097/MEG.0000000000000437>.
- 13 De Marchi S, Chiarioni G, Prior M, Arosio E. Young adults with coeliac disease may be at increased risk of early atherosclerosis. *Aliment Pharmacol Ther.* 2013;38(2):162–169. <https://doi.org/10.1111/apt.12360>.
- 14 Bonci E, Chiesa C, Versacci P, Anania C, Silvestri L, Pacifico L. Association of non alcoholic fatty liver disease with subclinical cardiovascular changes: a systematic review and meta-analysis. *Biomed Res Int.* 2015;2015:213737. <https://doi.org/10.1155/2015/213737>.
- 15 Reilly NR, Lebowitz B, Hultcrantz R, Green PH, Ludvigsson JF. Increased risk of non-alcoholic fatty liver disease after diagnosis of celiac disease. *J Hepatol.* 2015;62(6):1405–1411. <https://doi.org/10.1016/j.jhep.2015.01.013>.
- 16 Ahearn J, Shields KJ, Liu CC, Manzi S. Cardiovascular disease biomarkers across autoimmune diseases. *Clin Immunol.* 2015;161(1):59–63. <https://doi.org/10.1016/j.clim.2015.05.024>.
- 17 Malamut G, Cellier C. Complications of coeliac disease. *Best Pract Res Clin Gastroenterol.* 2015;29(3):451–458. <https://doi.org/10.1016/j.bpg.2015.05.005>.
- 18 Emilsson L, Lebowitz B, Sundström J, Ludvigsson JF. Cardiovascular disease in patients with coeliac disease: a systematic review and meta-analysis. *Dig Liver Dis.* 2015;47(10):847–852. <https://doi.org/10.1016/j.dld.2015.06.004>.
- 19 Kelly CP, Bai JC, Liu E, Leffler DA. Advances in diagnosis and management of celiac disease. *Gastroenterology.* 2015;148(6):1175–1186. <https://doi.org/10.1053/j.gastro.2015.01.044>.