CASE REPORT

Gluten-free diet: a possible treatment for chronic diarrhoea in common variable immunodeficiency

Joana Sofia Pita,¹ Rosa Anita Rodrigues Fernandes,¹ Rui Almeida,² Emilia Faria,¹ Carlos Loureiro,¹ Ana Todo Bom¹

¹Allergy and Clinical Immunology, Coimbra's University Hospital Centre, Coimbra, Portugal
²Pathology, Coimbra's University Hospital Centre, Coimbra, Portugal

Correspondence to
Dr Joana Sofia Pita,
joana.s.pita@gmail.com

Accepted 9 June 2018

SUMMARY

Gastrointestinal disorders are frequent in common variable immunodeficiency (CVID). Clinical symptoms and histological alterations in CVID can resemble celiac disease. Usually, patients with chronic diarrhoea associated with CVID do not improve with a gluten-free diet. The authors present a case of a male patient who was diagnosed with CVID at age 33 and had chronic diarrhoea which resolved after initiating a gluten-free diet. Clinical relapse occurred after gluten reintroduction. The main objective of this case report is to alert clinicians to implement a gluten-free diet in patients with CVID with chronic diarrhoea.

not.² Enteropathy in CVID is frequent and may be treated by immunosuppressive therapy.⁵ Typically, patients with enteropathy associated with CVID have neither clinical nor histological improvement with a gluten-free diet.^{5 7} This is an interesting case of a patient who had total resolution of his gastrointestinal symptoms by following a gluten-free diet, with clinical relapse with gluten reintroduction. According to the literature, clinical improvement after initiating a gluten-free diet is rare, and there is no histological improvement. This is a rare case due to the fact that we observed a clinical and histological improvement after gluten avoidance.

BACKGROUND

Common variable immunodeficiency (CVID) is a primary immunodeficiency with reduced levels of immunoglobulins (IgG, IgA and/or IgM) associated with a reduced antibody response.¹ This entity encloses a group of heterogeneous primary antibody failure syndromes characterised by hypogammaglobulinaemia, but one essential feature, common to all patients with CVID is loss of B-cell function.² The most common presentation of this disease is recurrent infections.¹ The precise prevalence of CVID is unknown, but it has been estimated at between 1:100 000 and 1:10 000 of the population.² Gastrointestinal disorders are frequent in CVID, and chronic diarrhoea can occur in 20%–60% of patients.¹ Enteropathy was found in 9% of the patients included in the European report.³ CVID enteropathy has an unclear pathogenesis. Small bowel biopsies show a mucosa with villous blunting and crypt distortion with increased lymphocytes (usually CD8 T cells), lymphoid hyperplasia and loss of plasma cells, the latter being a frequent histological feature in CVID.² It seems that the absence of plasma cells and increased lymphoid hyperplasia reliably distinguishes CVID enteropathy from celiac disease.⁴ Some authors suggest that human leukocyte antigen (HLA-DQ) markers in patients with CVID may help distinguish CVID enteropathy due to immune dysregulation, which means that if celiac disease markers are absent, a diagnosis of CVID enteropathy is more likely.⁵ The absence of these molecules has a negative predictive value for celiac disease close to 100%.⁶ Although Major histocompatibility complex (MHC) genetic tests may be helpful, blood analysis with dosing of transglutaminase and other antibodies usually are

CASE PRESENTATION

The authors present a case of a 50-year-old male patient, with a personal history of recurrent infections in childhood (otitis, tonsillitis), pneumonia and papillary carcinoma diagnosed at 30 years of age, submitted to total thyroidectomy and iodotherapy, orchitis and epididymitis at 41 years of age.

At 33 years of age, he was sent to our primary immunodeficiencies consultation for recent hypogammaglobulinaemia. In our consultation, he underwent blood analysis, and the most relevant results are shown in [table 1](#).

Diagnosis of CVID was performed after excluding other causes of hypogammaglobulinaemia (drug induced, infectious diseases, malignancy) based on the following criteria: frequent infections in childhood, hypogammaglobulinaemia (1.05 g/L) and a previous measurement of IgG 2.04 g/L 2 months before the consult, low IgA and IgM, and no response to vaccination.²

Analysis of B memory cells corresponds to a EUROclass B+ group (2% of B cells). Absence of switched B cells corresponds to a subgroup smB– (<2% of switched memory cells). This severe reduction of class-switched B-cell memory is associated with a significant decrease in serum IgG and IgA at the time of diagnosis.⁸ Right after the blood analysis, he was started on intravenous immunoglobulin at a dose of 25 g (0.4 mg/kg) with a monthly frequency. Despite the treatment with immunoglobulin and having normal levels of IgG 7.68 g/L, he still had chronic diarrhoea. Due to refractory symptoms, he was started on immunoglobulin reposition treatment at a frequency of 3–3 weeks (preinfusion levels were always evaluated and were ≥7 g/L), with no clinical improvement.

© BMJ Publishing Group Limited [2018]. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Pita JS, Fernandes RAR, Almeida R, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-225143

Table 1 Blood analysis performed in our consultation

Analysis performed at 33 years of age	
IgG	1.05 g/L
IgA	<0.07 g/L
IgM	0.02 g/L
Haemoglobin	15 g/dL
Platelet count	235x10 ⁹ /L
Total leukocytes	12.9x10 ⁹ /L
Lymphocytes	1.2x10 ⁹ /L
CD19	2%
Switched B memory cells	0%
B naïve	80%
CD4/CD8	0.42%
CD4	14%
CD8	56%
T regulatory cells	0.2%
Proteinogram	Decreased β and γ fractions
HIV, Hepatitis C Virus, Hepatitis B Virus serology	Negative
Serum albumin	Normal
Autoimmunity	Negative
Isohaemagglutinins	Negative
Antibody response to pneumococcal and tetanus vaccination	<0.33; <0.10

At age 44, he was admitted to our hospital with acute diarrhoea (7–10 dejections/day, without blood or mucus) for the last 30 days, abdominal distention, 8% weight loss in 2 months, muscle pain and fatigue.

The results of the workup performed in the internal medicine department are shown in [table 2](#).

The patient improved clinically after fluid therapy and corticotherapy and had clinical discharge after 17 days. After discharge, the patient irregularly followed a gluten-free diet, with numerous clinical relapses with ingestion of cereals. A few days after hospital discharge, he was submitted to a duodenal biopsy which showed areas of partial villous atrophy and presence of intraepithelial lymphocytes, lamina propria with inflammatory infiltrate (mononucleated cells, with some eosinophils and lymphoid aggregates). No evidence of *Giardia intestinalis* or *Cryptosporidium*. Eight months later, he was resubmitted to small intestine biopsies: duodenum and jejunum with flat, enlarged and blunted villi, irregular crypts, lamina propria with aggregated lymphocytes and neutrophils conditioning lesions of cryptitis and pericryptitis.

Table 2 Workup performed in the internal medicine department

Blood analysis and digestive tract endoscopy	
Potassium	2.4 mg/dL
Magnesium	1.4 mg/dL
Creatine kinase	13 718 U/L
Antideamidated gliadin IgA and IgG antibodies	Negative
Antireticuline and antitransglutaminase IgA antibodies	Negative
HLA DQ2/DQ8	Negative
Stool culture	Negative
Parasitological examination of stool	Negative
Traces of fat on stool sample	Negative
Endoscopy	No macroscopic lesions
Total colonoscopy	No macroscopic lesions

Figure 1 Small intestine biopsy showing villous atrophy, lamina propria with inflammatory infiltrate and intraepithelial lymphocytes (H&E x100).

Crypts with apoptotic bodies (basal portion) and numerous mitosis ('celiac disease-like' findings) ([figure 1](#)).

Immunohistochemistry showed B lymphocytes (CD20+) and T lymphocytes (CD3+) in the lamina propria, mostly intraepithelial (<44/100 enterocytes) ([figure 2](#)). Two years after this episode, he was submitted to a new colonoscopy which once again showed no macroscopic lesions. Small bowel biopsies under gluten-free diet showed a discrete chronic non-specific duodenitis ([figure 3](#)). He remained asymptomatic following a gluten-free diet. Skin prick tests and analysis performed in our consult are shown in [table 3](#).

OUTCOME AND FOLLOW-UP

The patient remained asymptomatic with gluten-free diet. When he occasionally had gluten-containing foods, he had diarrhoea (2–3 episodes a day, without mucus or blood) during the day of the ingestion and sometimes on the next day, with posterior resolution with gluten avoidance).

Nowadays, he is clinically stable, with no need for hospitalisation, and maintains intravenous immunoglobulin at a dose of 30 g once a month.

Figure 2 CD3 immunohistochemistry revealing increased intraepithelial T lymphocytes (>30/100 enterocytes)—CD3x200.

Figure 3 Duodenal mucosa with preserved architecture and unspecific mononuclear inflammatory infiltrate of lamina propria (H&E x100).

DISCUSSION

CVID is a primary immunodeficiency characterised by recurrent infections, autoimmunity and lymphoproliferative phenomena.⁹ Gastrointestinal symptoms are frequent in CVID (up to 60% of cases).^{1,9} Crohn's disease-like findings, as lymphoid nodular hyperplasia, villous atrophy, crypt hypertrophy and a T-lymphocyte infiltrate have been described.⁹ As previously stated by Morreale *et al*,⁹ in patients with CVID an alteration of the duodenal mucosa poses a difficult differential diagnosis that includes celiac disease. The diagnostic dilemma is that CVID and celiac disease may coexist in the same patient, associated with the fact that patients with CVID do not have an antibody response which means they are seronegative for celiac disease.

After duodenal biopsies, the patient started a gluten-free diet, assuming that he had a celiac disease associated with CVID. Gastrointestinal symptoms improved after this approach, and even after obtaining a negative HLA result, we recommended maintaining a gluten-free diet.

This measure was important in controlling chronic diarrhoea.

There is *in vitro* evidence in celiac and non-celiac experimental models - that gluten/gliadin might directly cause damage in epithelial cells due to non-immunomediated mechanisms.¹⁰ Gliadin causes cellular cytoskeleton rearrangement, loss of tight junctions, resulting in a permeability increase in duodenal and jejunal mucosa. It has a toxic effect in the small bowel due to the reduction of F-actin cellular content, it inhibits DNA and RNA synthesis, epithelial cell growth, oxidative stress and induces apoptosis.

Gluten can cause gastrointestinal abnormalities by increasing acetylcholine release and cholinergic activation which might lead to an increase in smooth muscle contractility.

All these facts led to maintaining a diet with cereal avoidance, with good clinical response.

Table 3 Skin prick tests and specific IgEs performed at 50 years of age

Prick tests	Results	Specific IgE	Results
Gluten	Negative	Gluten	Negative
Wheat	Negative	Wheat	Negative
Rye	Negative	Rye	Negative
Barley	Negative	Barley	Negative

In this specific patient with negative antibodies due to immunodeficiency, HLA DQ2/DQ8 helped to perform differential diagnosis. A negative result excludes the diagnosis of celiac disease in at least 95% (>95% negative predictive value).^{9,11} Based on these previous data, we assumed that celiac disease was not the most probable diagnosis.

Other differential diagnosis in this case is wheat allergy. Wheat allergy is frequent in atopic patients and has several diagnostic criteria: positive skin prick tests/prick-to-prick/specific IgE to wheat.¹¹ Our patient had negative results to prick tests and specific IgE to wheat (table 3); therefore, wheat allergy was excluded.

Another important entity is non-celiac gluten sensitivity (NCGS). NCGS is a diagnosis of exclusion, and it can be diagnosed in those patients with gluten intolerance with negative antibodies, normal/mild inflammation in duodenal mucosa and good clinical response to gluten-free diet.¹¹ NCGS is characterised by systemic symptoms that occur with gluten ingestion, disappear with gluten avoidance and relapse after gluten reintroduction. The typical presentation is a combination of systemic symptoms such as abdominal distention, joint and muscle pain, muscle contractions, chronic fatigue, body mass loss and anaemia.

According to what has been discussed above, the most likely diagnosis in this patient is a CVID associated with NCGS.

The described histological abnormalities after hospital discharge were observed in an acute phase of gastrointestinal disease associated with CVID which justifies the biopsy findings, corresponding to a period of gastrointestinal disease exacerbation and gluten ingestion. After several months of gluten avoidance, a biopsy was performed again, showing a discrete duodenitis, associated with a stable phase of CVID, without gastrointestinal symptoms.

Relapsing of symptoms with gluten reintroduction also suggests a gluten sensitivity.

Some previous studies describe patients with chronic diarrhoea associated with CVID and negative HLA DQ8/DQ2 markers who were submitted to a gluten-free diet. In these studies, only few had clinical improvement (2/12 cases) and none had histological response.^{5,7}

In this case, as the patient has an associated NCGS, we verified a good clinical response to gluten avoidance. Thus, this case is of extreme clinical importance, as it demonstrates that patients with CVID and chronic gastrointestinal symptoms can have another disease aggravating their gastrointestinal symptoms. It is important to emphasise the significant improvement of gastrointestinal symptoms when adhering regularly to a gluten-free diet.

Learning points

- Celiac disease is hard to diagnose in a patient with common variable immunodeficiency (CVID).
- The absence of HLA DQ2/DQ8 has a negative predictive value for celiac disease (CD) >95% which excludes CD in this patient.
- Despite the fact that CD markers were negative, this specific patient improved with gluten-free diet.
- It is important to implement a gluten-free diet in patients with CVID and chronic diarrhoea with negative stool cultures.
- Chronic refractory diarrhoea in patients with CVID can be associated to non-celiac gluten sensitivity.

Acknowledgements Dr. Emilia Faria, Dr. Carlos Loureiro and Professor Ana Todo Bom (assistant graduates in Allergy and Clinical Immunology) were essential in this article's critical revision and final approval.

Contributors I, Joana Sofia Pita declare that every cited author contributed to this case report. This patient was followed and treated by Dr. Joana Sofia Pita (main author), Dr. Rosa Anita Fernandes, and Dr. Emilia Faria, who followed this patient and worked on data collection, conception and design, acquisition of data, article drafting and writing. Our colleague from pathology, Rui Almeida, worked on microscopy and histology, contributing for a correct histological diagnosis. Dr. Carlos Loureiro and Professor Ana Todo Bom were essential for this manuscript drafting, final revision and approval.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Kobrynski LJ, Mayer L. Diagnosis and treatment of primary immunodeficiency disease in patients with gastrointestinal symptoms. *Clin Immunol* 2011;139:238–48.
- 2 Bonilla FA, Barlan I, Chapel H, *et al.* International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. *J Allergy Clin Immunol Pract* 2016;4:1.
- 3 Gathmann B, Mahlaoui N, Gérard L, *et al.* Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol* 2014;134:116–26.
- 4 Malamut G, Verkarre V, Suarez F, *et al.* The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. *Am J Gastroenterol* 2010;105:2262–75.
- 5 Venhoff N, Emmerich F, Neagu M, *et al.* The role of HLA DQ2 and DQ8 in dissecting celiac-like disease in common variable immunodeficiency. *J Clin Immunol* 2013;33:909–16.
- 6 Wolters VM, Wijmenga C. Genetic background of celiac disease and its clinical implications. *Am J Gastroenterol* 2008;103:190–5.
- 7 Gentile NM, Murray JA, Pardi DS. Autoimmune enteropathy: a review and update of clinical management. *Curr Gastroenterol Rep* 2012;14:380–5.
- 8 Wehr C, Kivioja T, Schmitt C, *et al.* The EUROclass trial: defining subgroups in common variable immunodeficiency. *Blood* 2008;111:77–85.
- 9 Morreale GC, Montalbano LM, Cappello M, *et al.* A difficult diagnosis of coeliac disease: Repeat duodenal histology increases diagnostic yield in patients with concomitant causes of villous atrophy. *Arab J Gastroenterol* 2017;18.
- 10 Mansueto P, Seidita A, D'Alcamo A, *et al.* Non-celiac gluten sensitivity: literature review. *J Am Coll Nutr* 2014;33(1):39–54.
- 11 Czaja-Bulsa G. Non coeliac gluten sensitivity - A new disease with gluten intolerance. *Clin Nutr* 2015;34.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow