



Clinical and nutrological aspects of celiac disease: a case report

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Abstract

Celiac Disease is an autoimmune enteropathy triggered by gluten intake in genetically predisposed individuals. The prevalence varies by country and it is estimated to be 1% of the population. Diagnosis can be made at any age, and may manifest in a typical manner with diarrhea, abdominal pain, malabsorption, malnutrition; or with atypical symptoms and extra intestinal manifestations such as metabolic diseases, and neurological symptoms. The interest in its diagnosis results in the regression of symptoms with the dietary exclusion of gluten, the recovery of adequate nutritional status, and the reduction of the risk of the appearance of more serious complications (refractory disease, lymphoma, and intestinal adenocarcinoma). A case is reported of a patient with Hashimoto's thyroiditis, with dyspeptic symptoms, ferropenia, and chronic fatigue who after an etiological investigation was diagnosed with celiac disease, in addition to reviewing current clinical, nutrological, and therapeutic aspects of the disease.

Keywords: Celiac disease. Diagnosis. Nutrological therapy.

Introduction

Celiac disease (CD) is an immune-mediated systemic enteropathy, triggered by gluten consumption, occurring in genetically predisposed individuals [1,2]. It is the T cell mediated immune response to ingested gluten that causes damage in carriers of the human leukocyte antigen (HLA) genes DQ2 and DQ8 [3]. It is estimated that up to 40% of the general population carries the susceptibility genes for developing the disease [4].

The entity is common worldwide and its prevalence has increased significantly over the last 20 years, varying from region to region, fluctuating between 0.5% and 1% in Europe and North America; it ranges from 2% to 3% in Finland and Sweden and has high rates in North Africa, the Middle East and Asia-Pacific regions [3,5].

In this sense, CD affects the proximal small intestine, but it can affect the entire small intestine, often resulting from its varied forms of presentation that can even include extradigestive manifestations and concomitantly with autoimmune diseases and malignant diseases. At the 14th International Symposium on Celiac Disease, held in Oslo in 2011, the entity was listed in different forms of presentation: classic, non-classical, subclinical, and asymptomatic, according to the symptoms [6] Classic, as the presence of intestinal malabsorption, with occurrence diarrhea, steatorrhea, vomiting, bloating, flatulence, weight loss, and failure to thrive; Non-classical: intestinal symptoms, but not involving malabsorption; are symptoms such as abdominal pain and constipation; Subclinical: the symptoms are extraintestinal, such as the presence of iron deficiency anemia (or iron deficiency), abnormalities in liver function, osteoporosis, among others; Asymptomatic: serological tests are positive, but there are no symptoms.

The presence of autoantibodies identifies individuals who should undergo a small bowel biopsy and is also useful for monitoring celiac patients. For diagnosis, it is essential to perform upper digestive endoscopy with small bowel biopsy (gold standard) in patients with positive serological test results or if there is a high clinical suspicion of celiac disease in the absence of positive serological test results. It is recommended to collect at least one or two biopsy

specimens from the duodenal bulb (from the 9 o'clock or 12 o'clock position, as it increases sensitivity [by almost 10%] in adults) and at least four from the post-bulbar duodenum (because the distribution of lesions is discontinuous) [3,7,8].

Given this, the present study reported a clinical case of a patient with Hashimoto's thyroiditis, dyspepsia, iron deficiency, and chronic fatigue who, after etiological investigation, was diagnosed with celiac disease, in addition to reviewing current clinical, nutritional, and therapeutic aspects of the disease.

Methods

Study Design

The present study was elaborated according to the rules of the CARE case report (<https://www.care-statement.org/>). A descriptive literature review was also carried out to provide sufficient scientific data for the theoretical basis of this study. The descriptors used were *Celiac disease. Diagnosis. Nutrological therapy*. The most relevant works to the proposed theme were selected, excluding those that did not contemplate the objective of this study. The research for the literature review was carried out from April to May 2023 and developed based on Google Scholar, Scopus, PubMed, Scielo, and Cochrane Library.

Ethical Approval

This study respected the human rights rules of the 1964 Declaration of Helsinki and obtained the Informed Consent Form according to CNS/CONEP Resolution 466/12 from Brazil. Data from the patient under study were obtained through the collection and analysis of information contained in the patient's medical record. The Informed Consent Form was applied.

Case Report

Patient Information and Clinical Findings, Timeline, Diagnostic Assessment, Therapeutic Intervention, and Follow-up

Female patient, 32 years old, white, nulliparous, referred for evaluation of the chronic dyspeptic condition, iron deficiency, and recurrent lesions on the skin of the lower limbs, lasting up to 72 hours. She reported a long history of abdominal discomfort, flatulence, and constipation, accompanied by chronic fatigue and easy tiredness. No other associated relevant signs or symptoms. Among the personal antecedents, Hashimoto's Thyroiditis (HT) and cases of mild iron deficiency anemia stand out. Regarding relevant family history: no history of chronic digestive diseases.

On physical examination, she was in good general condition, with normal-colored mucous membranes. At the level of the lower limbs, palpable purpura lesions stood out in the distal third (Figure 1). Weight of 76 kg and height of 165 cm for a body mass index (BMI) of 27.9 kg/m², and body surface area of 1.8 m² overweight. Her abdomen revealed mild tympany, no pain, and no palpable mass.

Figure 1. Vasculitis.



Analytically, he presented normochromic normocytic anemia (hemoglobin 11.2 g/dL), hematocrit 33.3%; global leukocytes 4320; platelets 273000; VHS: 26mm/1st hour; CRP: 0.19 mg/L; folic acid 4.4 ng/mL; 25 OH Vitamin D 10.69 ng/mL; Serum iron 49mg/dL; Ferritin: 19ng/mL, IST 18%, were slightly low. Vitamin B-12 343 pg/ml; Zinc 73.61ng/dL; TSH: 16.44 nIU/mL; Free T4: 0.85ng/dL; Anti-thyroglobulin antibody greater than 1000.0 IU/m; AntiThyroid Peroxidase Antibody 944 IU/mL; Non-reactive Neutrophil Cytoplasmic AntiCytoplasmic (ANCA). Fasting glucose, urea, creatinine, bilirubin, and hepatic cytolysis enzymes were normal. Total cholesterol and triglycerides are normal. Serologies for hepatitis B, C, HIV, and HSV viruses were negative. Parasitological examination of feces and fecal occult blood test were negative.

In an initial imaging evaluation, the patient underwent magnetic resonance imaging (MRI) of the abdomen and pelvis, which showed "Liver with areas of focal steatosis, densification of the adipose planes of the mesenteric root, with prominent lymph nodes suggestive of mesenteric panniculitis. No evidence of other alterations" Bone densitometry (BMD) was within the range expected for age.

In the second consultation, the indicated tests were evaluated: the lactose tolerance test: Baseline (95 mg/dL), 30 minutes (104 mg/dL), 60 minutes (103

mg/dL), and 98 minutes (88 mg/dL), Total IgA 289; Anti-Transglutaminase IgA Higher than 128 Elia IU/mL, and Antiendomysial IgA Antibody Reagent 1/160 (Table 1).

Table 1. Summary of analytical changes.

EVALUATED PARAMETERS	RESULTS	REFERENCE VALUE
Hemoglobin	11.2	12.0 to 15.0 g/dL
serum iron	49	50 to 170ug/dL
ferritin	19	10.0 to 291.0 ng/mL
IST	18 %	20 to 50 %
VHS	26 mm	Less than 20 mm
25(OH)D	10 ng/mL	>60 years Greater than 20 ng/mL
TSH	10.43 nUI/mL	<60 years and risk group 30 to 60 ng/mL
Anti-Thyroglobulin Antibodies	Greater than 1000.0 IU/mL	0.40 to 4.30 nUI/mL
Antiperoxidase Antibodies	1198 IU/mL	Less than 4.5 IU/mL
Lactose Tolerance Test	Basal 95 mg/dL 30 minutes 104 mg/dL 60 minutes 103 mg/dL 90 minutes 98 mg/dL	Up to 60 IU/mL
Anti-transglutaminase IgA antibody	Greater than 128.0 Elia U/mL	Any value above 20 mg/dL in relation to the baseline value will be considered normal.
IgA Antiendomysial Antibody	Reagent 1/160	Negative: Less than 7.0 Elia U/mL

The patient was evaluated by a hematologist and dermatologist; exams performed: Immunofixation, absence of monoclonal band; Anti-Cardiolipin IgM and IgM negative; Protein electrophoresis Polyclonal hypogammaglobulinemia, Gamma Globulin 23% (11.8 to 18.8%) 1.75g/dL (0.72 to 1.27g/dL), INR Ratio 1.21 (0.80 to 1.20), APTT Ratio 1.27 (<1.25), Von Willebrand Factor Antigen 103% (50 to 160%); with the diagnostic conclusion of vasculitis of probable immunological etiology. In the context, an upper digestive endoscopy (UDE) was performed with a biopsy of the duodenum, which showed "bulbar mucosa with atrophy associated with areas of enanthema, a second duodenal portion that exhibits diffuse atrophy associated with villi with a dentate appearance" (Figure 2).

Figure 2. Upper digestive endoscopy.

Figure 2A. duodenal bulb.



Figure 2B. Second duodenal portion.



The anatomopathological study of the duodenal biopsy revealed "Duodenal bulb: complete villous atrophy ("Flat mucosa"), intraepithelial lymphocytes increased more than 40 IE per 100 enterocytes. Marsh-Oberhuber classification 3C (Table 2).

Table 2. Anatomopathological classification Marsh Oberhuber.

Injuries	Diagnostic criteria
Type I lesion infiltration	No architectural changes (preserved villus/crypt ratio) Increased IEL count (>25/100 epithelial cells)
Type II hyperplastic lesion	No architectural changes (villous/crypt ratio preserved) crypt hyperplasia (mitosis > 1/crypt) Increased IEL count (> 25/100 epithelial cells)
Type III injury A destructive injury	Villous atrophy

	(mild grade) Crypt hyperplasia (mitosis > 1/crypt) Increased IEL count (> 25/100 epithelial cells)
Type III B destructive injury	Villous atrophy (moderate degree) Crypt hyperplasia (mitosis > 1/crypt) Increased IEL count (> 25/100 epithelial cells)
Type III C destructive injury	Villous atrophy (severe degree) Crypt hyperplasia (mitosis > 1/crypt) Increased IEL count (> 25/100 epithelial cells)

CD diagnosis was based on clinical history and serological, endoscopic, and histological results. Lactose intolerance was secondary to damage to the brush border of the intestinal mucosa, iron deficiency, mild anemia, and vitamin D deficiency, resulting from the alteration of the absorptive surface.

The beginning of a gluten-free diet (GFD) and trace elements (microelements: selenium, copper, zinc, fluorine, manganese) was indicated, with specific guidelines to avoid crosscontamination. After about four months of follow-up, the patient strictly adheres to a glutenfree diet and follows detailed guidelines to avoid cross-contamination; significant improvements in dyspeptic symptoms appear. Eight weeks after starting iron therapy and Vitamin D replacement, there was a slight response in hemoglobin, iron deposits, and 25(OH)D levels. In continuous use of oral iron (ferripolymaltose) tablets of 325 mg and with 100 mg of elemental iron, in divided doses, twice a day, for eight weeks, hemoglobin increased to 11.9 g/dL. Vitamin D replacement with a weekly dose of 50,000 IU for eight weeks raised the initial value to 20 IU/mL. The withdrawal of lactose from the diet was indicated and calcium supplementation was also instituted. A new serology will be performed when completing the sixth month of the onset of the GFD.

Discussion

The CD is considered one of the most common disorders of the digestive tract. Typically described in children, more and more adults express the disease, coursing with extremely varied intestinal and/or extraintestinal conditions. The prevalence is approximately 1% of the world's population and has a high distribution variation between countries, being strongly influenced by genetics. Studies also show a prevalence of 1% in a population not studied [9].

In Brazil, the regions with the highest prevalence are the South and Southeast, influenced by the strong European colonization, but also by the greater availability

and access to diagnostic methods compared to other Brazilian regions. One in 474 adults and one in 184 children develop undiagnosed CD. The incidence of CD in individuals aged 1 to 14 years is 5.44 per 1,000 people. In adults, the number is 2.11 per 1,000, showing that CD is not a rare disease in our country and has rates similar to those in Europe [10]. In so-called high-risk groups, the disease is more prevalent: such as type 1 diabetes (1-12%); autoimmune thyroid disease (2-6%); Down Syndrome (2-6%); autoimmune hepatitis (3- 7%); Turner syndrome (4-5%); first-degree relatives with CD (10-20%); individuals with iron deficiency anemia (3-15%); patients with osteoporosis (1-3%), among other clinical conditions [5,11]. The clinical case described corresponds to a patient with an initial diagnosis of HT, with the presence of thyroid autoantibodies and no family history of autoimmune diseases or chronic intestinal diseases. HT is the most prevalent thyroid disease of all and is also the autoimmune disease most associated with other endocrinopathies; in the present case, the presence of anti-thyroperoxidase (anti-TPO) and antithyroglobulin antibodies, with high levels of thyroid-stimulating hormone (TSH), confirm the diagnostic criteria [7,12].

Studies consulted demonstrate that 5%-15% of patients with CD have hypothyroidism, with a risk four times greater than that of patients in control groups; CD, in turn, occurs in 2%-5% of patients diagnosed with autoimmune thyroiditis, also more prevalent than in control groups. So, it is suggested that patients with autoimmune thyroiditis should be investigated for celiac disease and vice versa, but the pathogenesis of this association is still uncertain and requires further investigation [13].

In the meta-analysis by Sun et al. [13], the prevalence of thyroid disease in CD patients was significantly higher when compared to controls, suggesting and confirming that CD patients should be screened for thyroid disease. The patient studied had a long history of abdominal discomfort, constipation, and weakness, associated with recurrent iron deficiency. The CD is increasingly recognized in the adult population without diarrhea, with a higher percentage of patients presenting as asymptomatic individuals, often detected in screening tests. However, some individuals experience constipation, recurrent vomiting, or heartburn, which can be confused with a functional disorder or Irritable Bowel Syndrome [14,15].

In addition to the classic form (malabsorption), the other recognized forms of presentation of CD are the asymptomatic (or silent) form, which is the typical glutensensitive enteropathy, but with the absence of clinical manifestations. Another form is the classic (or

atypical) form, characterized by a monosymptomatic or paucisymptomatic picture, with onset later in childhood; patients may have isolated manifestations such as short stature, iron deficiency anemia refractory to treatment, arthritis, or arthralgia, seizures, tooth enamel hypoplasia, dermatitis herpetiformis, hypertransaminasemia, precocious puberty, recurrent abdominal pain, and constipation [16].

The patient in the study had constipation and this symptom is an atypical and uncommon clinical manifestation in review articles; however, proven descriptions of constipation as a symptom of this disease, available in the literature, are rare.

Nutritional deficiencies resulting from malabsorption of macro and micronutrients, such as iron, folic acid, vitamin B12, and calcium deficiency, involve the appearance of symptoms. As iron absorption generally takes place in the small intestine, especially in the duodenum, in CD this portion (duodenum) is most frequently affected, resulting in a reduction in iron absorption and subsequent iron deficiency anemia. The patient had maintained an unexplained iron deficiency with frequent use of oral iron, and low levels of vitamin D were detected. Iron deficiency is often the only clinical sign of CD, especially in patients with subclinical/atypical forms.

In a systematic meta-analysis, Mahadev et al. [16] identified 18 studies, including 2,998 patients (adults and children) with iron deficiency anemia, finding CD in 3.2-5.5% of individuals. In a recent literature review of several studies focused on the prevalence of AF in celiac patients, Talarico et al. [17] conclude that iron deficiency anemia is the most frequent extraintestinal manifestation of CD, with a prevalence between 12% and 82% of celiac patients. Therefore, CD should be investigated in all adults with unexplained iron deficiency anemia, due to its association with the chronic inflammatory state and malabsorption of micronutrients.

Talarico et al. [17] confirm that the primary treatment for CD is GFD, which is associated with adequate management of iron deficiency anemia, if present. Iron replacement has been based on oral products containing ferrous sulfate, however, its absorption is limited in patients with active CD and unpredictable in patients on GFD. In addition, poor tolerability of ferrous sulfate is particularly frequent in patients with CD or other inflammatory bowel diseases. Normalization of the anemic state usually occurs after at least six months of GFD, but the process can take up to two years for iron stores to be replenished.

Another symptom reported by the patient was fatigue, which is common in CD, with an incidence of up to 37% at diagnosis and of multifactorial etiology.

Chronic fatigue may be an indication for CD screening, as it has been found more frequently among undiagnosed CD cases [18].

During the initial interview, the patient reported recurrent episodes of skin lesions on both lower limbs, which, after specific examinations, were interpreted by the hematologist and dermatologist as a vasculitis of probable autoimmune etiology. There are few reports of cutaneous vasculitis associated with CD. In the extensive bibliographic survey carried out, few articles were found describing the vascular phenomenon as a symptom and/or rare manifestation of CD. Vasculitis is a term that refers to damage and inflammation of the walls of blood vessels of any size. It is one of the rare extraintestinal complications of CD. Other known neurological presentations are acute generalized chorea and pseudotumor cerebri, all of which appear to be responsive to GFD [18,19].

Clinical features of leukocytoclastic vasculitis include palpable purpura, nodules, hemorrhagic vesicles, bullae, and livedo reticularis, distributed mainly in the lower extremities [19]. There are sporadic reports on the association between CD and cutaneous vasculitis. The coexistence of these two entities may be related to increased intestinal permeability and immune complexes, originating from exogenous or endogenous antigens, which may circulate due to the impaired phagocytic function of the reticular endothelial system and be deposited in the skin [20].

Meyers et al. [21] described the case of a 38-year-old woman with cutaneous vasculitis associated with CD and the remission of the cutaneous lesions after treatment with a restricted GFD. Therefore, GFD treatment may improve cutaneous vasculitis lesions in CD-associated cases. In case of evidence of symptoms or signs of the classic and atypical forms of CD and for individuals at risk, the measurement of human recombinant antitransglutaminase (TTG) antibody of the IgA class and immunoglobulin A (IgA) should be requested simultaneously. If both dosages are normal, the individual's involvement with CD is unlikely at the moment. The patient had positive Anti-tTG and AEM, with a strong suspicion of CD. EDA was performed with a small bowel biopsy, which closed the diagnosis of CD.

The histological diagnosis of the CD consists of an integrated assessment of the following elementary lesions [1,2,6]:

- ✓ Increased intraepithelial T-lymphocytes: a value of 25 T-lymphocytes/100 enterocytes is considered a pathological condition also called "lymphocytosis";
- ✓ Crypt hyperplasia: extension of regenerative epithelial crypts associated with the presence of more than 1 mitosis per crypt;

- ✓ Villous atrophy: decrease in the villous height, alteration of the normal cipher/villous ratio (3:1) until the total disappearance of the villi. None of these elementary lesions is specific for CD; the diagnosis of CD is based on the identification of histological alterations accompanied by consistent clinical and serological data. Based on the presence of one or more of these elementary lesions, DC histopathology is subdivided into different diagnostic categories according to the Marsh Oberhuber classification (Table 2).

The diagnosis of CD should also always be kept in mind when a patient presents with an unexplained and isolated hematological finding. Once diagnosed, patients should adhere to GFD and be educated about the possible complications of this disease [16]. Once the diagnosis is confirmed, the adoption of multidisciplinary and multi-professional care for individuals with CD is recommended, involving, in addition to physicians, nutrition, psychology, and social work professionals. A lifetime GFD is a treatment for individuals with CD. Continuing to eat gluten can exacerbate clinical symptoms, further intestinal damage, and increase the risk of future cancers, including small intestinal adenocarcinoma, esophageal cancer, melanoma, and non-Hodgkin's lymphoma [2].

Complete removal of gluten-containing foods from the diet, including gluten proteins in wheat (gliadin), barley (hordeins), rye (secalin), oats (avenins), and other closely related grains, is the first indication; and incorporating other nutritious food sources such as fruits, vegetables, fish, meat and gluten-free products. The habit of looking at and analyzing product labels before consuming them is necessary for patients with CD [22].

Another very important issue is the threat of cross-contamination, a daily situation for individuals with a GFD; occurs when there is a direct or indirect transfer of physical, chemical, or biological contaminants from a food, utensil, vector, or handler to food that will be consumed (it can occur during pre-preparation, treatment, storage, transport, service). Other sources of contamination are sponges, dish towels, wooden spoons, and frying oil, among others [2,5,23].

A GFD can be monitored using several methods that allow monitoring and evaluating its adherence and effectiveness. It can be followed by evaluating the symptoms. Another option would be the dietary interview to assess self-compliance with the GFD. Another element may be the serological assessment in which serological markers represent the body's immune response to the disease, as they are not directly correlated with intestinal damage; making serology an

unreliable marker for following mucosal adherence and monitoring [5,18].

Other monitoring methods are stool and urine markers, which are rarely used by physicians. And finally, small bowel biopsy and pathology, which currently evaluates small bowel pathology and is the most accurate method to monitor mucosal recovery in patients on a GFD. Although complete histological recovery is not universally achieved in a GFD, several studies suggest that mucosal healing can be seen in 57%-76% of patients [18,24].

Tests showed lactose intolerance due to the small bowel brush border injury, clinically related to the patient's discomfort, a feeling of fullness, and flatulence. The total withdrawal of dairy foods from the diet is cause for concern; these foods are primary sources of calcium, and the body loses considerable amounts of this mineral daily. This requires a constant supply of calcium from other dietary sources to ensure bone mineral density. Another form of diet therapy is enzymatic replacement with exogenous lactase (+ β -galactose) obtained from yeasts and fungi [25].

Lactose intolerance is a clinical syndrome that occurs after lactose ingestion and includes one or more of the following symptoms: abdominal pain, diarrhea, nausea, flatulence, and/or abdominal distension [26]. CD and lactose intolerance are relatively frequent diseases with symptoms that occur after ingestion of certain food components. In CD, therapy is a lifelong GFD, and in lactose intolerance, treatment is based on reducing the dietary intake of lactose. Although this reduction is recommended to relieve symptoms, it can lead to nutritional disadvantages due to reduced intake of calcium and vitamins [27].

Nutritional deficiencies of iron, vitamin D, calcium, B12, and folic acid, should be treated immediately with appropriate drug therapy for their correction. In particular, vitamin D deficiency has several consequences, notably secondary hyperparathyroidism, which is found in 19% to 28% of individuals with CD and can progress to primary hyperparathyroidism if left untreated; some patients with initial normocalcemic hyperparathyroidism subsequently develop hypercalcemic hyperparathyroidism despite vitamin D repletion and gluten avoidance [18]. Most deficiencies can be restored with (longterm) treatment with GFD and/or nutritional supplementation [25].

Conclusion

Celiac disease diagnosis is complex, especially in asymptomatic patients or with atypical manifestations. In the presence of unexplained iron deficiency anemia,

or the presence of autoimmune diseases with digestive symptoms, celiac disease screening is always necessary. An intestinal biopsy is necessary for the diagnosis of celiac disease, even if the serology is positive. The only treatment to date for celiac disease is definitive gluten-free diet, and immediate replacement of the micronutrient deficiency. The celiac patient requires multidisciplinary and specialized follow-up.

Acknowledgement

Not applicable.

Ethical Approval

This study respected the human rights rules of the 1964 Declaration of Helsinki and obtained the Informed Consent Form according to CNS/CONEP Resolution 466/12 from Brazil. Data from the patient under study were obtained through the collection and analysis of information contained in the patient's medical record. The Informed Consent Form was applied.

Informed consent

The patient alongside their legal guardian signed the consent form.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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