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Case report

Type 1 Refractory Celiac Disease: Report of Two Cases with Different Therapeutic Approaches

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Abstract

Background: Lifelong strict adherence to a gluten-free diet (GFD) is the effective treatment for celiac disease (CD), leading to symptom remission and mucosal healing. Refractory celiac disease (RCD) is defined as the persistence or relapse of symptoms and intestinal damage in individuals previously diagnosed with CD after at least 12 months of strict GFD adherence, occurring in a minority of CD patients. Diagnosis and differentiation of RCD type are performed via specific immunohistochemistry on duodenal biopsy. **Case 1:** A 52-year-old male with a prior CD diagnosis presented with persistent symptoms even after five years of strict GFD adherence. He was diagnosed with type 1 refractory RCD and treated with oral budesonide (9 mg/day for 8 months), achieving clinical remission, with normalization of duodenal mucosal histopathology. **Case 2:** A 62-year-old female with a prior CD diagnosis and two years of strict GFD adherence presented with severe symptoms. She was diagnosed with type 1 RCD and treated with azathioprine at 2 mg/kg/day for 24 months, resulting in complete symptom remission and restoration of duodenal mucosal integrity. **Conclusions:** In addition to strict adherence to a healthy gluten-free diet, both oral budesonide and azathioprine were effective in treating type 1 RCD, as patients achieved and maintained clinical remission without drug-related adverse effects. Histological response, demonstrating complete normalization of duodenal mucosal architecture, confirmed the success of therapy.

Keywords

Celiac disease, treatment, diagnosis, gluten-free diet, budesonide, azathioprine.

INTRODUCTION

Celiac disease (CD) is a permanent immune-mediated disorder of T cells, triggered and maintained by the ingestion of gluten present in wheat, barley, and rye in genetically susceptible individuals. Strict, lifelong adherence to a gluten-free diet (GFD) is the cornerstone of effective treatment for CD, leading to symptom remission and mucosal healing within 12 months[1-3]. However, in a minority of patients, full clinical and mucosal recovery does not occur, and symptoms may persist despite strict adherence to a gluten-free diet[4]. Approximately 15% of patients on a GFD never recover[5]. Non-responsive celiac disease (NRCD), which affects 7% to 30% of individuals with CD on a GFD, is defined as persistent symptoms, signs, or laboratory abnormalities typical of CD despite strict adherence to a GFD for 6 to 12 months[6,7]. If NRCD is suspected, confirmation of the initial CD diagnosis is mandatory, as is the absence of any intentional or unintentional gluten consumption, and re-evaluation of duodenal histopathology[1,2,6]. At the same time, differential diagnosis is crucial to investigate other diseases that overlap with CD and cause similar symptoms[1-3,7].

Persistent villous atrophy without evidence of gluten contamination may indicate a subset of patients who are sensitive to very small amounts of gluten (hypersensitive). Patients are considered to have a slow response when complete recovery may occur between 18 and 29 months on a gluten-free diet (GFD). However, in cases of slow healing, refractory celiac disease (RCD) should be investigated[1-7]. This is defined as the persistence or relapse of symptoms and intestinal damage in individuals previously diagnosed with celiac disease, after at least 12 months of strict adherence to a GFD[6]. RCD is classified into two types based on molecular and immunophenotypic characteristics[8,9]. Flow cytometry is recommended for the differential diagnosis between the two forms, RCD1 and RCD2. For this purpose, the biopsy set must be preserved in saline solution and not in formalin[8,9]. In type 1 RCD (RCD1), intraepithelial lymphocytes (IELs) are polyclonal expansions of T cells with a normal phenotype (surface CD3+ and CD8+)[8,9]. In these cases, steroids, preferably budesonide, and immunosuppressive drugs such as azathioprine (AZA) can be prescribed[10]. Type 2 RCD (RCD2), on the other hand, is characterized by clonal expansions of IELs with an aberrant phenotype (surface CD3-, cytoplasmic CD3+, and CD8-), which is associated with higher morbidity and mortality[8]. Treatment may include steroids like budesonide, and prednisone is an alternative if budesonide is not available; however, immunosuppressants are not indicated in these cases[10].

Therefore, defining the type of RCD is crucial in clinical practice to plan the appropriate treatment and consider the prognosis[2,6,8,11]. In Brazil, there is only one reported case of RCD2[12].

Here we report two cases of RCD1 showing the patients' clinical and laboratory findings and treatment plan.

METHODS

This study was approved by the Institutional Ethics Committee under protocol 4770592. It is a retrospective study conducted through a review of medical records. The same physician treated the patients at a private medical office in the city of Curitiba, Brazil, and the same pathologist evaluated the biopsies.

Extradigestive and gastrointestinal symptoms at the time of RCD diagnosis were investigated from transcripts of patients' subjective reports. Routine laboratory tests were required to determine the patients' nutritional status and diagnose disorders that could overlap with CD. Serum levels of immunoglobulin A (IgA) and anti-transglutaminase IgA (anti-tTG) were measured to assess adherence to a GFD.

All patients underwent an upper gastrointestinal endoscopy. Duodenal biopsies were performed according to the following recommendations: 1 or 2 fragments from the bulb (at the 9 and 12 o'clock positions) and 4 to 5 samples from the duodenum[1,13]. Samples were fixed in 10% formalin to standardize histological examination. CD was classified using the Marsh-Oberhuber score[14,15]. Furthermore, upon clinical suspicion of RCD, an immunohistochemistry method with anti-CD3 and anti-CD8 antibodies was performed on paraffin sections[9,16]. A colonoscopy was required for diagnosis, exclusion of microscopic colitis[17] and malignancies[18,19]. Imaging exams were required to allow for the early detection of small lesions and EATL (enteropathy-associated T-cell lymphoma). DEXA (dual-energy X-ray absorptiometry) was used to assess bone disease.

CASE REPORTS

Case 1

A 52-year-old Caucasian male with a previous diagnosis of CD presented with symptoms even after 5 years of strict adherence to a GFD. He presented with asthenia, weight loss, diarrhea, aphthous ulcers, and gastroesophageal reflux. Laboratory results showed decreased serum vitamin D levels and fecal elastase. However, serum concentrations of negative anti-tTG IgA, iron, vitamin B_{12}, and albumin were normal. The patient reported a previous diagnosis of lactose intolerance. Exocrine pancreatic insufficiency was also diagnosed. He was undergoing treatment for osteoporosis. Colonoscopy revealed a polyp detected in the sigmoid colon, and histopathology indicated a tubular adenoma without dysplasia.

Case 2

The case involves a 62-year-old Caucasian female with a previous diagnosis of CD and two years of strict adherence to a GFD, yet she presented with severe symptoms. She reported bloating, weight loss, diarrhea, aphthous ulcers, gastroesophageal reflux, epigastric pain, nausea, and flatulence. Laboratory results showed decreased serum levels of iron, vitamin B_{12}, and vitamin D. Furthermore, anti-tTG IgA was negative, and serum albumin was normal. The patient reported a previous diagnosis of lactose intolerance, asthma, hypothyroidism, and breast tumor ablation several years prior to the CD diagnosis. Exocrine pancreatic insufficiency was diagnosed. She was also undergoing treatment for osteoporosis. Colonoscopy results were normal.

Imaging tests (computed tomography [CT] or magnetic resonance imaging [MRI]) showed no abnormalities in either case. DEXA confirmed osteoporosis in both patients.

Table 1 shows the histopathological findings of the duodenal mucosa before and after treatment.

Table 1. Histopathological findings of the duodenal mucosa before and after treatment

Test	Case 1	Case 2
Biopsy at CD diagnosis*	Marsh III-C	Marsh III-C
Duration of GFD treatment	5 years	2 Years
Biopsy at RCD diagnosis	Marsh III-A	Marsh III-B
Immunohistochemistry	RCD1	RCD1
Treatment (period)	Budesonide (8 months)	Azathioprine (24 months)
Biopsy after treatment	Marsh 0	Marsh 0
Immunohistochemistry	Normal	Normal

*Marsh-Oberhuber classification. GFD: gluten-free diet; CD: celiac disease; RCD1: type 1 refractory celiac disease. Table prepared by the authors.

In Case 1, oral budesonide was administered at a dose of 9 mg/day, divided into three doses of 3 mg each, based on the findings of Mukewar et al.[20]. The rationale for this approach is that oral budesonide likely provides adequate drug delivery. With this administration form, budesonide is distributed uniformly throughout the small intestine. Budesonide is available in 3 mg hard gelatin capsules containing the prescribed medication. The active drug is contained within an insoluble ethylcellulose polymer, which provides time-dependent release of budesonide. It is hypothesized that opening the gelatin capsule and crushing the drug in the teeth will initiate the release of budesonide from the ethylcellulose polymer matrix, resulting in a more immediate action in the proximal small intestine[21]. This regimen was used for 8 months, at which point clinical remission was achieved and duodenal mucosal histopathology showed normality (**Figure 1**). The patient reported no side effects.

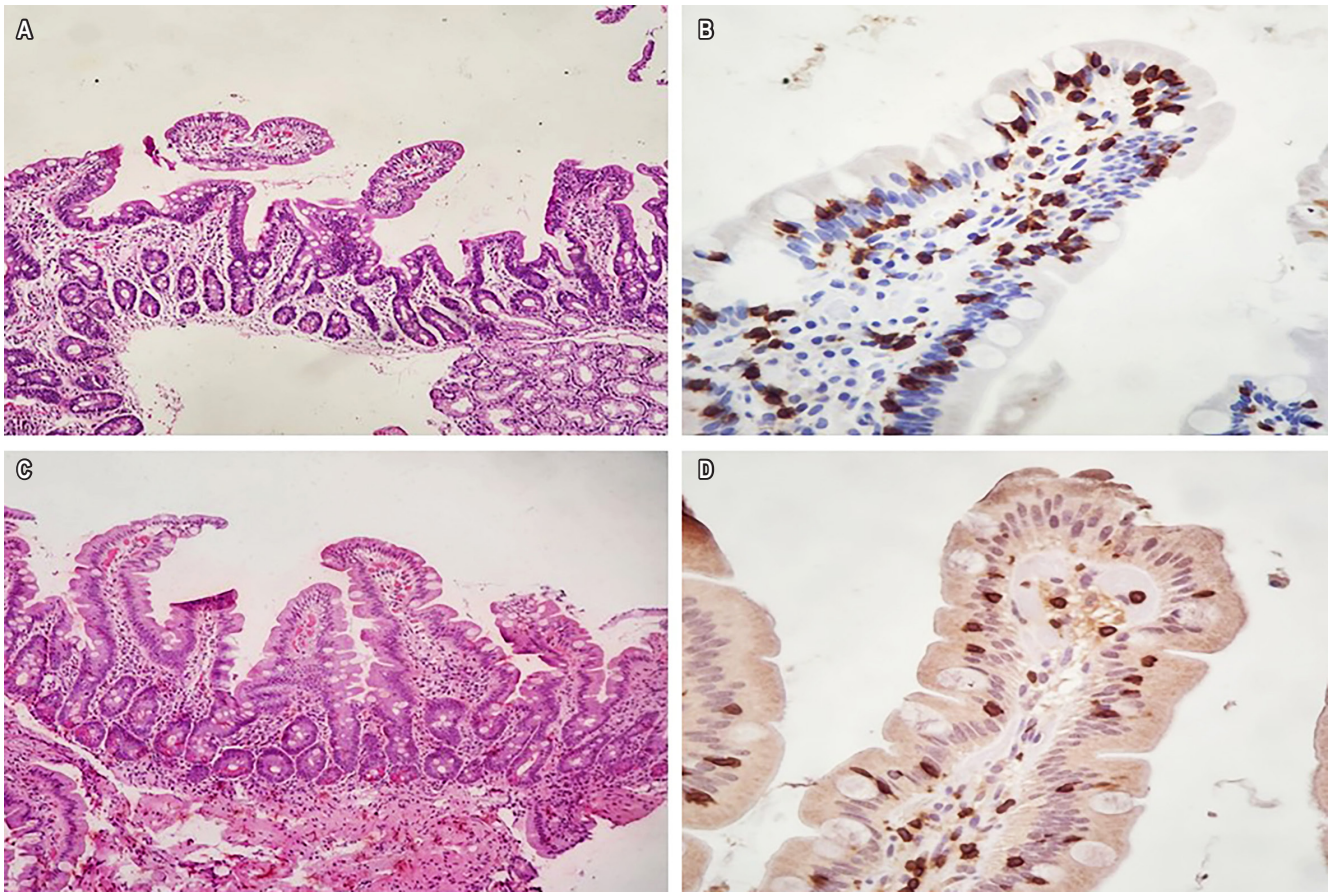

Figure 1. Histopathology of the duodenal mucosa. **A.** Duodenal biopsy before treatment; hematoxylin-eosin showing Marsh 3-A (100X). **B.** Immunohistochemistry before treatment showing a high number of IELs: CD8 >50% of IELs, compatible with type 1 RCD (400X). **C.** Duodenal biopsy after treatment; hematoxylin-eosin showing Marsh 0 (100X). **D.** Immunohistochemistry after treatment showing a normal CD8 count (400X). Images property of the authors.

For the second case, since the patient had previously used prednisone for asthma, azathioprine was initiated at a dose of 2 mg/kg/day. This improves the effect of steroids and allows for lower doses. Goerres et al.[10] used azathioprine to treat patients with RCD1, starting with an induction therapy of prednisone. The benefit could result from the therapeutic effect of both agents and avoiding the side effects of prednisone, through the steroid-sparing effect of azathioprine[10]. The total duration of treatment for azathioprine has not yet been established, although Goerres et al. recommended one year[10]. Iqbal et al.[23] reported a case where azathioprine was used for seven years. Azathioprine was discontinued at 24 months because the patient was asymptomatic and had regained her pre-CD diagnosis weight. Her laboratory tests were normal, and the duodenal mucosa had returned to Marsh-0 (**Figure 2**). The patient reported no side effects.

DISCUSSION

It is extremely important to alert treating physicians that the differential diagnosis between NRCD and RCD is crucial in those patients who adhere to a GFD yet maintain symptoms. RCD generally occurs after the age of 50[6], as was also found in our patients. RCD can be clinically classified as primary (patients who showed no clinical/histopathological improvement from the time a GFD was initiated) or secondary (patients who experienced a sudden clinical worsening after many years of a very good response to a GFD)[8]. The cases described in this report fall into the latter group.

Before labeling a patient as having RCD, it is mandatory to confirm whether the initial CD diagnosis was correct[2,6]. In our cases, a re-evaluation of the duodenal histopathology was requested and CD was confirmed. Classifying RCD

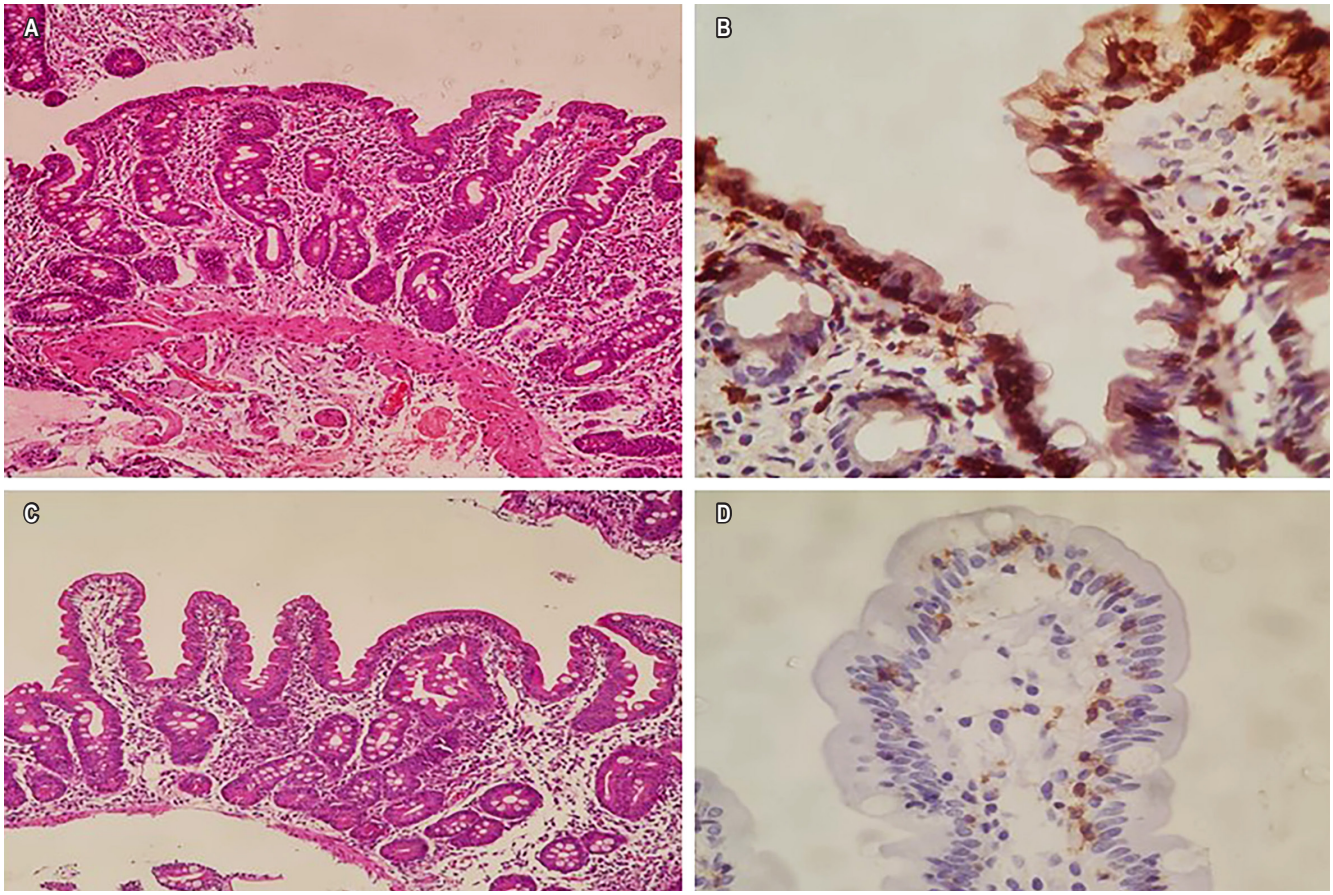

Figure 2. Histology of the duodenal mucosa. **A.** Duodenal biopsy before treatment; hematoxylin-eosin showing Marsh 3-B (100X). **B.** Immunohistochemistry before treatment showing a high number of IELs: CD8 >50% of IELs, compatible with RCD1 (400X). **C.** Duodenal biopsy after treatment; hematoxylin-eosin showing Marsh 0 (100X). **D.**Immunohistochemistry after treatment showing a normal CD8 count (400X). Images property of the authors.

as type 1 or 2 is crucial for treatment and prognosis[8,11]. Although cytometric analysis of IELs with an aberrant phenotype is considered the gold standard, the diagnosis of RCD can be confirmed by immunohistochemistry[9,16], as was performed in our case studies.

When CD is confirmed after strict adherence to a GFD for at least 12 months, the serological level of anti-tTG IgA can be negative or positive at low levels[6]. In our patients, anti-tTG IgA levels were negative, suggesting strong adherence to a GFD, as reported by the patients.

Macro- and micronutrient deficiencies are common in CD at the time of diagnosis and during treatment. Deficits in iron, vitamin B_{12}, and vitamin D were detected in our patients. The GFD combined with dietary support, as well as the repletion of detected mineral/vitamin deficiencies and the treatment of comorbidities, resulted in an improvement of the clinical picture.

In the presented cases, the diagnosis of NRCD was suspected at the first appointment considering the clinical presentation after 5 years (Case 1) and 24 months (Case 2) of strict adherence to a GFD with duodenal histology showing Marsh III-C. Disorders potentially overlapping with CD were ruled out. Since individuals on a GFD who have persistent symptoms have a significantly higher rate of exocrine pancreatic insufficiency (28.4%)[24], pancreatic elastase levels were determined. Both patients had lower levels and were prescribed pancreatic enzyme replacement.

Requesting immunohistochemistry on the duodenal biopsy is essential to differentiate between type 1 and type 2 RCD, and this result is crucial for defining treatment and prognosis. The treatment of RCD involves close monitoring of the GFD, aggressive nutritional support, and immune suppression to reduce inflammation in the small intestine[25]. Regarding prescribed medications, oral budesonide is recommended as the first line of treatment, followed by azathioprine[10]. Raiteri et al.[26] reported a relatively high level of agreement among guidelines from different scientific societies for treating RCD.

Regarding the disease prognosis, RCD1 has a positive and excellent response to steroids and immunosuppressive drugs, as shown in our cases, and a very good 5-year survival outcome, ranging from 80% to 96%, which is the expected outcome for our patients[2,6,11]. Both patients continue under follow-up.

CONCLUSION

In addition to strict adherence to a GFD, both oral budesonide and azathioprine were effective in the treatment of RCD1, as the patients achieved and maintained clinical remission without drug side effects. The histological response, which showed complete normalization of the duodenal mucosal architecture, confirmed the success of the therapy.

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