Complete Resolution of Type 1 Refractory Celiac Disease after Combined Treatment with Budesonide and Azathioprine: A Case Report and Literature Review

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Abstract Refractory Celiac Disease is a rare condition associated with a substantial mortality rate. Both treatment and follow-up are still matter of debate. The case of a 54 year-old man with refractory celiac disease is presented who required treatment with both budesonide and azathioprine. A concise review of the clinical Management of Refractory Celiac Disease is then performed.

Keywords: celiac disease, diet, gluten free, lymphoma

1. Introduction

Refractory celiac disease (RCD) is a rare condition that is associated with both high complication and mortality rates. Immunosuppressants have been proposed as a therapeutic option; however, evidence is scarce and treatment as well as follow up of this condition is still a matter of debate. A case of a celiac disease (CD) patient that developed a type-1 RCD that was treated with combination therapy with budesonide and azathioprine is presented.

2. Case Report

A 54 year-old man was admitted to our institution due to severe diarrhea and hypokalemia that started two weeks before admission. He was diagnosed of CD two years ago: he presented positive IgA anti-transglutaminase (tTG) antibodies (252 U/ml) on diagnosis as well as total villous atrophy (Marsh IIIC) on duodenal biopsies. On admission, the patient was pale, with a marked abdominal distention and peripheral oedema. Laboratory results revealed microcytic anemia (Hb= 9.5 gr/dl; MCV= 75), K+= 2.7 mEq/l, hypoalbuminemia (2.8 gr/l). Anti-tTG as well as anti-endomysium and anti-gliadin antibodies were negative; HIV serology was negative and IgG levels were slightly increased. Nutritional assessment confirmed strict adherence to gluten-free diet (GFD). Upper endoscopy showed typical villous atrophy endoscopic findings and colonoscopy showed no relevant findings. Duodenal biopsies showed severe villous atrophy with increased...
number of intraepithelial lymphocytes (IELs >30/HPF) and ruled out findings compatible with Whipple’s disease or giardiasis. Colon biopsies excluded microscopic colitis. Stool analysis ruled out the presence of Giardia or other parasites. CT-enteroclysis showed a significant thickening of the jejunal wall; capsule endoscopy was performed (Figure 1) which revealed multiple ulcers throughout the proximal jejunum, compatible with ulcerative jejunitis. PET Scan did not show any abnormal tracer uptake. Single-balloon enteroscopy was undertaken in order to take multiple jejunal biopsies: immunophenotype analysis did not show aberrant IELs: these expressed surface CD3, CD8 and TCR-β and without TCR rearrangement (Figure 2). A diagnosis of type-1 refractory celiac disease (RCD) was done.

![Figure 2. Jejunal biopsy with immunohistochemical analysis](image)

![Figure 3. Second capsule endoscopy performed after treatment](image)
Treatment with 9 mg of budesonide was initiated. After clinical improvement, the patient was discharged. After two months of treatment, the patient did not experienced complete resolution of his symptoms. Azathioprine was then added at a 2 mg/kg dose. Budesonide dose was slowly tapered. After six months of combined treatment, a complete resolution of symptoms was achieved; the patient continued on azathioprine treatment. After twelve months, CT-enteroclysis was normal and a capsule endoscopy was repeated, which showed a complete endoscopic resolution of jejunal ulcers (Figure 3). Repeat endoscopy showed a significant histological improvement. Azathioprine treatment was discontinued.

3. Discussion

CD is a chronic inflammatory disorder that affects the small intestine in genetically susceptible individuals [1]. It is caused by the ingestion of gluten present in cereals such as wheat, barley and rye, and improvement is usually observed after initiation of a strict GFD [2]. Non-responsive CD is defined as the lack of clinical and/or histological improvement after 6-12 months of GFD; in many cases, inadvertent exposure to gluten may be the cause [3], but in a small percentage of cases, malabsorptive symptoms may be due to persistent villous atrophy and severe inflammation despite strict adherence to GFD: this is known as RCD [4].

RCD is typically divided into two subgroups: types 1 (RCD 1) and 2 (RCD 2). The distinction of these categories is based on the detection of abnormal intraepithelial lymphocyte phenotype (which is the hallmark of RCD 2): this is determined by the presence of aberrant lymphocytes using CD3/CD8 immunochemistry and T-cell receptor (TCR) clonal rearrangement (by means of polymerase chain reaction or flow cytometry). The characterization of aberrant T-cells seems to have a prognostic impact, since it is a strong predictor of enteropathy-associated T-cell lymphoma (EATL) [5]. Thus, RCD 2 carries a poorer prognosis, with an elevated short-term mortality [6]. The prognosis of RCD 1 is much better as compared to RCD 2; it is based on the detection of abnormal intraepithelial lymphocyte phenotype and is known as RCD [4].

Follow-up should be strict and thorough: apart from repeated intestinal biopsies, a complete evaluation of the small intestine seems to be relevant. For this matter, Capsule Endoscopy offers an useful and non-invasive tool for this purpose. CT-enterography may be another option; in this case, we found a good correlation between tomographic and capsule endoscopic findings before and after treatment.

4. Conclusions

This case report describes a patient with a diagnosis of RCD 1 that was successfully treated with a combined treatment of budesonide and azathioprine after an initial treatment of budesonide. It was also documented the value of capsule endoscopy and CT-enterography as follow-up tools in this kind of patients.

References


