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Should Small Intestine Bacterial Overgrowth be Ruled out as a Cause of Non-Responsive Celiac Disease?: A Case Report

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Abstract Non-responsive celiac disease is defined as the persistency of symptoms, signs or laboratory abnormalities typical of CD despite 6-12 months of dietary gluten avoidance. Small intestine bacterial overgrowth has been classically considered a potential cause for non-responsive celiac disease. Nevertheless, the evidence regarding its prevalence among non-responsive celiac patients is conflicting, as well as the evidence showing a benefit in small intestine bacterial overgrowth treatment in this clinical setting. We report the case of a 34 year-old woman diagnosed with non-responsive celiac disease in spite of adequate gluten-free diet, that had complete resolution of symptoms after treatment with antibiotics for small intestine bacterial overgrowth.

Keywords: *celiac disease, small intestine bacterial overgrowth, diet, Gluten-Free*

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1. Case Report

A 34 year-old woman was diagnosed with celiac disease (CD) twelve months ago. She had a history of Hashimoto's thyroiditis. CD was diagnosed in the context of iron-deficiency anemia (Hb 11 gr/dl) and diarrhea. She had positive tissue-transglutaminase IgA antibodies (IgA tTG= 100 UI/L) as well as positive anti-endomysium antibodies. Duodenal biopsies showed severe villous atrophy (Marsh IIIC - Figure IA).

The patient started a gluten-free diet (GFD) upon diagnosis. After a mild improvement of symptoms that lasted six months, she had a recurrence of watery stools and abdominal bloating. A thorough evaluation of GFD compliance was undertaken, showing no inadvertent gluten intake. Laboratory analysis showed a correction of anemia (Hb 12 gr/dl; Ferritin 40 ug/mL) and IgA tTG values within normal range. Human Immunodeficiency Virus serology was negative and immunoglobulin levels were normal.

Due to the persistency of symptoms, an upper endoscopy was performed, showing isolated duodenal scalloped folds. Duodenal biopsies showed no proliferation of aberrant lymphocytes as well as an improvement in villous atrophy severity (Marsh II - Figure 1B). Colonoscopy with colonic mucosa biopsies in order to rule out microscopic colitis was also undertaken, showing no abnormalities. A capsule endoscopy did not show any noticeable lesions in jejuno-ileal mucosa. An independent pathologist was invited to compare the last biopsies made with those made at diagnosis in a blinded fashion: total villous atrophy was found at diagnosis and the last biopsies showed only an increase of intraepithelial lymphocytes.

Finally, a lactulose breath test was performed, showing an increase in hydrogen excretion of more than 30 parts per million before 90 minutes (Figure 2). These findings were suggestive of small intestine bacterial overgrowth (SIBO). Hence, treatment with rifaximin 550 mg b.i.d. for two weeks was administered. Sustained resolution of symtpoms was achieved after finishing antibiotic treatment.

2. Discussion

Non-responsive CD is defined as the persistency of symptoms, signs or laboratory abnormalities typical of CD despite 6-12 months of dietary gluten avoidance [1]. There is a wide variation in the description of its prevalence, ranging from 7 to 30% [2,3]. The diagnosis of non-responsive CD is relevant because it may represent the development of Refractory CD, a rare condition with a poor prognosis [4].

The most common cause of non-responsive CD is the ingestion of gluten, whether it is inadvertent or voluntary. Nevertheless, there are some differential diagnosis that should be ruled out, such as microscopic colitis [5]. SIBO has been described as one of these [6].

SIBO is caused by an abnormal number of bacteria in the small intestine, owing to different predisposing conditions, such as impaired motility or failure of the

gastric-acid barrier [7]. Usual definition implies a total growth of $\geq 10^5$ colony forming units per ml (cfu/ml), but this is not a universally acepted definition. SIBO has been related to some gastrointestinal disorders, such as Irritable Bowel Syndrome [8].

The gold standard for the diagnosis of SIBO is aspiration and culture of jejunal contents, but it is difficult to perform and to reproduce. Hence, indirect methods such as breath tests using different substrates (such as glucose or lactulose) have been proposed as diagnostic tools [9]. These tests have the advantage of being non-invasive, but on the contrary have many pitfalls, specially in their arbitrary interpretation.

The exact prevalence of SIBO in CD is not well known, and this may be because of the limitations in diagnosing SIBO, as aforementioned. Tursi et al [10] found a high prevalence of SIBO (66.66%) in 15 non-responsive CD patients. This concept is reinforced by the case reported by Goshal et al [11]. It is worth mentioning that, apart from the small number of patients evaluated, SIBO was assessed by means of breath tests in both studies. What is more, CD may be related to increased hydrogen excretion levels, whether they are related to SIBO or not. According to Corazza et al [12], fasting hydrogen excretion in untreated CD was significantly higher than healthy controls, treated CD and similar to that of subjects with SIBO.

Rubio-Tapia et al [13] evaluated the prevalence of SIBO in non-responsive, non-diagnosed and responsive CD by means of jejunal aspirate culture. They found a global prevalence of 9.3% of SIBO in this population, which were distributed in the non-responsive and in the undiagnosed CD population. This results contrast with the suggestions made by the previously mentioned studies, making SIBO prevalence not as high as initially supossed in non-responsive CD. Nevertheless, since jejunal aspirate culture is difficult to perform and may be biased, these results may underestimate the true prevalence of this condition in this clinical setting.

If evidence assessing SIBO prevalence in CD subjects is not abundant, evidence evaluating SIBO treatment in non-responsive CD is even rarer. Chang et al [14] published a double-blinded, randomized controlled trial conducted in non-responsive CD patients in order to evaluate the efficacy of rifaximin on persistent gastrointestinal symptoms. After a 10-day treatment with rifaximin or placebo, no significant differences were found in symptom presence and severity as well as in breath tests results before and after treatment.

It would be interesting to perform another set of duodenal biopsies after treatment with rifaximin in order to evidence any potential improvement in histological features. However, we performed an analysis of already performed biopsies by a pathologist in a blinded fashion, showing a significant improvement after GFD. This finding, together with the result of capsule endoscopy, emphasizes the fact that symptom occurrence was not due to persistency of intestinal inflammation due to gluten exposure.

Limited evidence makes it mandatory to search for more well-designed clinical trials as well as well-conducted studies assessing the exact prevalence of this condition among CD subjects. Empirical treatment with antibiotics such as rifaximin or other non-absorbable antibiotics could be useful in CD patients with persistent symptoms; however, it would be necessary to develop diagnostic strategies in order to discriminate which patients would benefit from this strategy.

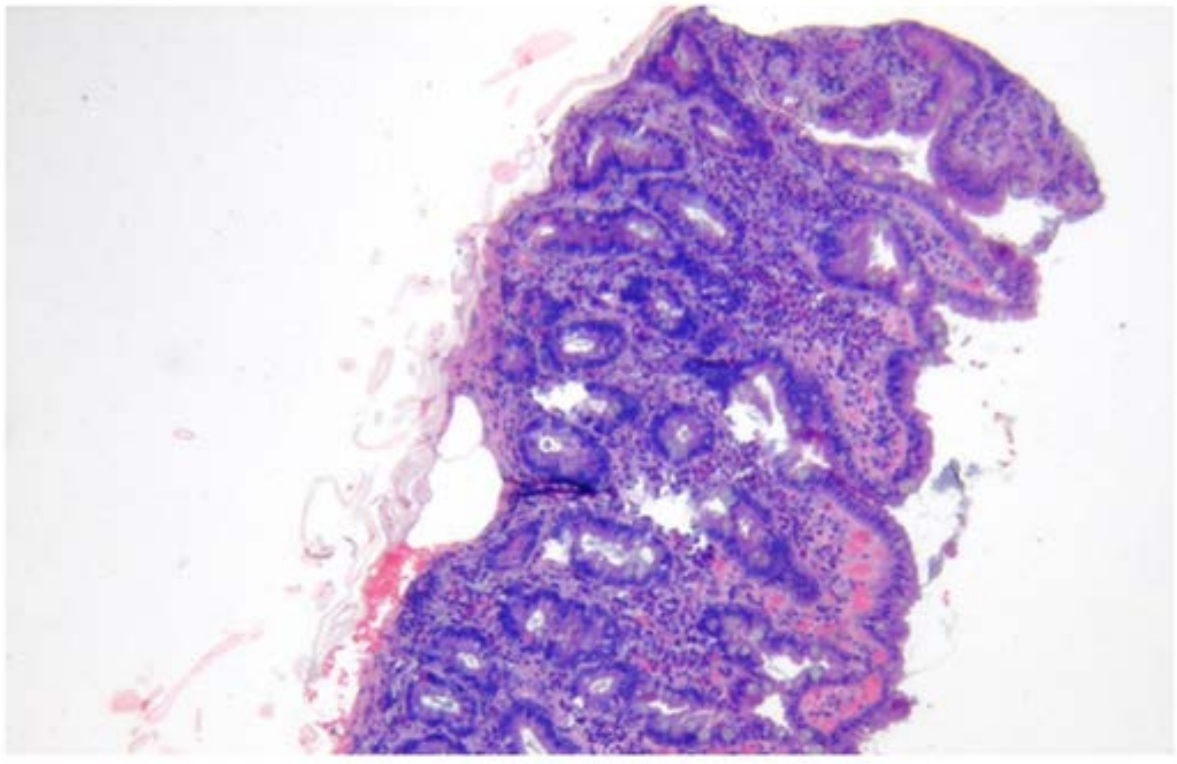

Figure 1A

Figure 1A. Duodenal biopsies showed severe villous atrophy (Marsh IIIC – Figure 1A)

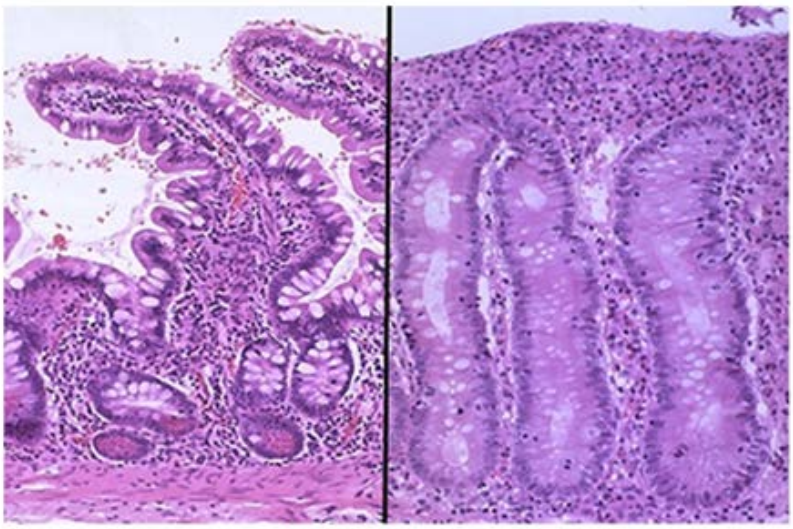

Figure 1B

Figure 1B. Duodenal biopsies showed no proliferation of aberrant lymphocytes as well as an improvement in villous atrophy severity (Marsh II – Figure 1B)

TIEMPO (en Minutos)	PPM
0	3
20	2
40	29
60	32
80	41
100	68
120	85
140	92
160	78
180	86

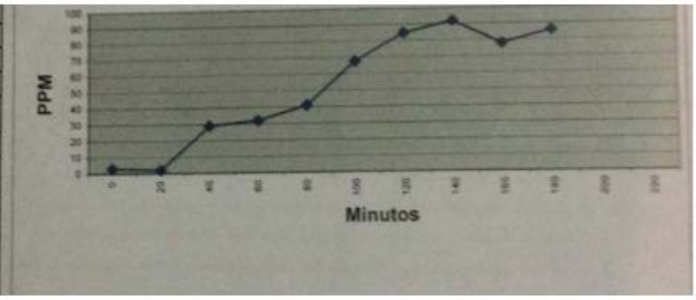

Figure 2

Figure 2. Finally, a lactulose breath test was performed, showing an increase in hydrogen excretion of more than 30 parts per million before 90 minutes (Figure 2)

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