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A Milligram of Gluten a Day Keeps the Mucosal Recovery Away: A Case Report

Federico Biagi, MD, Jonia Campanella, MD, Susi Martucci, MD, Donatella Pezzimenti, MD, Paul J. Ciclitira, PhD, Heather J. Ellis, PhD, and Gino R. Corazza, MD

In recent years it has been suggested that patients with celiac disease can be adequately followed up on the basis of merely clinical and serological response to a gluten-free diet. Thus, a duodenal biopsy some months after commencement of a gluten-free diet would no longer be necessary. We report here the case of a celiac patient in whom the ingestion of a milligram of gluten every day for 2 years prevented histological recovery in spite of satisfactory clinical and serological response. The literature regarding the minimal amount of gluten that could be harmless to celiac patients is reviewed.

Key words: celiac disease, gluten-free diet, gliadin, villous atrophy, endomysial antibody

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Introduction

Celiac disease is a gluten-induced enteropathy for which treatment consists of permanent withdrawal of gluten from the diet.[1] In spite of some provocative papers,[2] adherence to a gluten-free regimen is crucial not only for intestinal mucosal recovery but also for the prevention of complicating intestinal T-cell lymphoma, the main cause of the increased mortality rate observed in celiac disease.[3] The Codex Alimentarius Commission of the World Health Organization (WHO) and the Food and Agricultural Organization of the United Nations (FAO) creates regulations governing foods labeled as gluten-free. This institution has recently proposed a new, but not conclusive, standard that allows the inclusion of up to 200 mg/kg (200 ppm) gluten in foods labeled "gluten-free."[4]

Drs. Biagi, Campanella, Martucci, Pezzimenti, and Corazza are with the Gastroenterology Unit, IRCCS Policlinico S. Matteo, University of Pavia, Italy. Dr. Ciclitira and Ellis are with the Gastroenterology Department, Rayne Institute, KCL, St. Thomas' Hospital, London, United Kingdom.

Nevertheless, we still have scant evidence regarding the minimal amount of gluten that could be defined "safe" for all celiac patients. In vivo challenge studies[5,6] have demonstrated a linear relationship between dose of gluten and extent of mucosal damage, showing that 100 mg/day of gliadin for 1 month is enough to produce histopathological changes on jejeunal celiac mucosa.[6] However, it is unknown whether a smaller but sustained quantity of gluten can damage intestinal mucosa in patients with celiac disease. This is a crucial point because compliance with a gluten-free diet may be hampered by a number of factors, including inadvertent gluten intake. Reportedly, up to 6% of foods that are supposed to be "gluten-free" on the basis of labeled indications contain more than 300 mg gliadin/kg product.[7] In young patients, a strict gluten-free diet is made more difficult by lack of supervision at school, the inevitable social implications, and the unpleasant taste of some gluten-free foods.[8] Finally, for many individuals, Holy Communion constitutes regular gluten intake. Consumption of only a tiny fragment of communion wafer was proposed and debated as a possible compromise between medical and theological matters.[9–11]

A clear consensus regarding the correct follow-up for treated celiac patients is still lacking.[12] According to some authors, a follow-up duodenal biopsy should always be taken.[13] However, others consider clinical improvement and seroconversion to be reliable markers of response to dietary restriction, making a second duodenal biopsy unnecessary.[1,14]

Here we report the case of a patient with celiac disease, for whom a minimal but daily dose of gluten over a 2-year period was sufficient to hamper mucosal recovery in spite of satisfactory clinical and serological response, fulfilling the revised European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) criteria.

Case Report

A 32-year-old religious woman was admitted to a hospital in August 1998 complaining of diarrhea, abdominal

pain, and weight loss (body mass index [BMI, kg/m^2] = 19). She had a history of iron deficiency anemia over the last 10 years with fatigue, hair loss, and koilonychia treated by intravenous iron supplementation. She reported failure to thrive in childhood and late menarche. Laboratory analysis revealed iron deficiency anemia (Hb = 10 g/dL; serum iron = 3.7 μmol/L; ferritin = 5 ng/L). Levels of folate were reduced, and vitamin B_{12} was normal. Liver function tests showed mildly raised transaminases. A flat small bowel mucosa on upper endoscopy and positive endomysial antibodies proved she was affected by celiac disease. HLA typing revealed DQA1*0501 DQB1*0201 susceptibility alleles.

Thereafter, she commenced a gluten-free diet. She was referred to our center in December 1999. Diarrhea and abdominal pain had stopped and weight lost had been recovered. Transaminases were normal. However, anemia and endomysial antibodies were still present. An interview revealed she was not on a strict gluten-free diet because she was taking a daily communion wafer and had several other unintentional dietary lapses. Although we explained to her how to follow a strict gluten-free diet, she refused to stop taking a daily fragment of communion wafer.

The fragments of communion wafer weigh approximately 30 mg each (Figure 1). The amount of gliadin was measured by a double-sandwich ELISA. As previously described, we used a murine monoclonal antibody PN3 (IgG1 subclass) raised against a putative toxic peptide (core sequence QQQPFP), and a polyclonal rabbit (IgG fraction) anti-unfractioned gliadin acting as capture antibody (50 mcg/mL).[15] The mean amount of gliadin was found to be 1.76 g gliadin/100g, corresponding to 3.52 g gluten/100g. A 30-mg fragment of communion wafer therefore contains approximately 0.5 mg of gliadin (1 mg of gluten).

Eighteen months later, apart from the daily intake of a small fragment of communion wafer, the patient was on a strict gluten-free diet, as assessed by a dietary diary. Her diet consisted of almost exclusively natural rather than manufactured products. The only exceptions were some gluten-free products approved by the Italian Celiac Society. However, multiple duodenal biopsies revealed persistence of severe villous atrophy and an increased number of intraepithelial lymphocytes (sections were blindly evaluated by an observer unaware of the timing of the biopsies). Nevertheless, at that time she was well, anemia had disappeared, and celiac antibodies were negative (Table 1). It should be noted that an 18-month period was suggested as a reasonable timing to perform a second duodenal biopsy, avoiding the risk of confusing slow-recovery patients with unresponsive patients.[16]

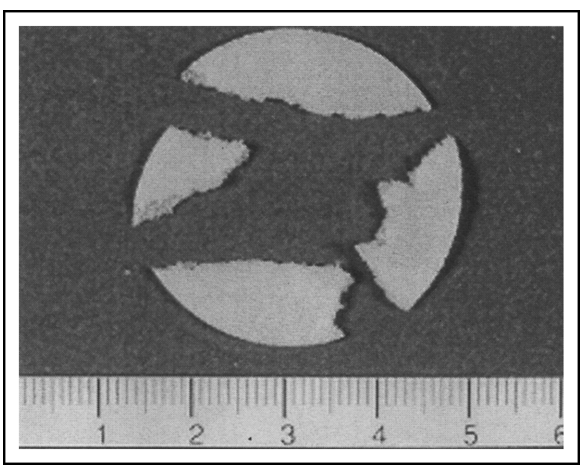

Figure 1. Fragments of communion wafer that underwent analysis of gluten content.

Discussion

Although the diagnosis of celiac disease requires that intestinal mucosa are shown to be gluten sensitive, a clear consensus on how to follow up with patients with celiac disease has not been reached so far.[12] To avoid the distress of a duodenal biopsy in young patients, pediatricians have suggested follow-up in young children simply on a clinical and serological basis.[1] However, endomysial antibodies have already been demonstrated to be a poor predictor of persisting villous atrophy.[17–19] Moreover, in patients undergoing oral challenge, while the intraepithelial lymphocyte count was found to be strictly related to gluten intake, clinical and laboratory data did not give any information.[6] We would caution that these data suggest that in patients on a low-gluten diet seroconversion of celiac antibodies can occur in spite of persistent mucosal abnormalities.

On histopathological grounds, no differences have been described between patients on a traditional gluten-free diet and those who follow a more rigorous diet, the so-called no detectable gluten (NDG) diet.[20] However, it is difficult to make an accurate comparison between the amount of gluten ingested daily by the patient we described and the amount of gluten present in both a gluten-free diet and an NDG diet. Inter-individual variability might explain differences in terms of gluten susceptibility. Another crucial point is that celiac patients following a gluten-free diet or an NDG regimen were all well treated and small bowel mucosa had recovered. One could speculate that a minimal quantity of gliadin can hamper mucosal recovery, but cannot induce villous atrophy in well-treated celiac patients. Although it is clear that a dose of 100 mg/day of gliadin administered for 1 month is toxic to duodenal mucosa,[6] to date, there are no studies investigating the effects of smaller doses of gliadin ingested for longer periods of time. Such

Table 1. Serologic, Histopathologic, and Dietary State at Diagnosis and Follow-up

Date	Hb (g/dL)	EMA	TTA	IgA AGA	IgG AGA	DII Bx	Diet
12/99	10.0	+	+	+	bdl	not done	GCD
01/00	10.3	−	bdl	−	bdl	Marsh 3	GFD + DCW
04/00	11.0	−	bdl	bdl	bdl	Marsh 3	GFD + DCW
07/00	12.1	−	bdl	−	bdl	Marsh 3	GFD + DCW
06/01	13.5	−	bdl	−	bdl	Marsh 3	GFD + DCW

Hb = hemoglobin, EMA = endomysial antibodies, TTA = tissue transglutaminase antibodies, AGA = gliadin antibodies, DII Bx = biopsy in the second part of duodenum, GCD = gluten-containing diet, GFD = gluten-free diet, DCW = daily communion wafer, − = negative, + = positive, bdl = borderline.

studies would better reproduce unintentional dietary lapses.

The case we presented suggests that the daily intake of 0.5 mg of gliadin for a 2-year period did not allow mucosal recovery. We are aware that the patient's diet could have been contaminated by undetected gluten. Only the dietary withdrawal of the fragment of communion wafer would have definitely clarified whether such a small amount of gluten was responsible for the lack of mucosal recovery. Unfortunately, the patient refused to take a gluten-free communion wafer. The Catholic church requires a communion wafer to be made with wheat flour. It is unlikely that the lack of mucosal recovery was due to gluten inadvertently contaminating her diet. The strictness of the patient's diet was assessed by a dietary diary and was comparable to that of the Italian Celiac Society patients, who respond histologically very well to a gluten-free diet. Finally, the patient's remarkably good clinical condition makes it very unlikely that she is affected by refractory/complicated celiac disease, a severe disease with a very poor prognosis.[21,22]

It should be noted that without the aid of a duodenal biopsy during the follow-up, we would have missed the lack of mucosal recovery, in spite of both clinical and serological response, fulfilling the revised ESPGAN criteria.[1] Mucosal recovery is the main protection against the occurrence of intestinal lymphoma.[3] We believe that in adult patients with celiac disease, a second duodenal biopsy should be made in all cases; this is the only way to identify patients with persisting villous atrophy, which could be missed if one relied on clinical and serological data only.

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