Markers of systemic and gut-specific inflammation in celiac disease

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Dear Editor,

Celiac disease (CD) is an enteropathy that is characterized by chronic malabsorption. The pathogenesis of CD involves immune-mediated injury to the mucosa of the small bowel. However, the correlation of CD with the systemic and gut-specific markers of inflammation remains unknown. This study reports the case of a patient who presented with features of systemic inflammation and autoimmunity and was subsequently diagnosed with CD. Importantly, it was observed that adhering to a gluten-free diet normalized these markers, suggesting a relationship between CD activity and systemic inflammation.

Here we describe the case of a 34-year-old female with vitamin D deficiency, along with an incidental detection of polyclonal hypergammaglobulinemia via serum protein electrophoresis (SPEP) during her routine blood work. Furthermore, fecal calprotectin and anti-transglutaminase antibody (anti-TTG) levels were also ordered as part of the investigation of this abnormality. Both tests came back strongly positive, with a fecal calprotectin level of 1450 µg/g and an anti-TTG titer of >100 U/mL (Table 1). Aside from the SPEP findings, hypergammaglobulinemia was also detected in the immunoglobulin panel. The patient's ANA titer was slightly positive, and she exhibited indications of iron deficiency. Moreover, other than a history of stress-induced vomiting during adolescence and occasional constipation, she did not have any other GI complaints. Furthermore, the patient reported that she had not used any non-steroidal anti-inflammatories or any other medications in the last 6 months and did not have a family history of CD. An esophago-gastro-duodenoscopy (EGD) was performed after being referred to the gastroenterology department. EGD revealed severe scalloping, atrophy, and fissuring of the proximal duodenum, which was deemed "highly suspicious" and an indicator of underlying CD. Biopsy specimens confirmed the presence of villous atrophy, as well as chronic inflammatory changes in the lamina propria with increased intraepithelial lymphocytes, confirming CD. Because of the very high fecal calprotectin, a colonoscopy was recommended to the patient, which she declined. However, because she lacked symptoms of IBD or a family history of IBD, and had a confirmed diagnosis of celiac disease, we did not pursue colonoscopy immediately. Instead, the patient agreed to undergo colonoscopy if her treatment for celiac disease did not result in marked improvement of the inflammatory biochemical parameters.

The patient was asked to follow a strict gluten-free diet and was followed-up after three months. She remained asymptomatic from a gastrointestinal standpoint, and her weight remained stable. Furthermore, the initial lab tests were repeated, and they revealed an improvement in her hypergammaglobulinemia, complete normalization of her fecal calprotectin, and her ANA had also normalized. After following the new diet for eight months, her anti-TTG titers were normal, iron deficiency had resolved, and her gamma globulins were normal. Serum protein electrophoresis also exhibited a "normal pattern." However, her bone mineral density revealed osteoporosis.

Thus, we describe the first adult case of CD with the traditional findings of TTG positivity and vitamin deficiency, along with elevated systemic and gut-specific inflammatory markers, which markedly responded to a gluten-free diet within 3-8 months. Interestingly, fecal calprotectin was the first of these markers to normalize despite the very high initial count, preceding both the gammopathy and TTG normalization.

The association between CD and other autoimmune disorders has been reported (1). Beyond autoimmune thyroid

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Table 1. Comparison of laboratory values prior to the diagnosis and after initiating a gluten-free diet.

Biomarker (reference range)	Prior to diagnosis	3 months on gluten free diet	8 months on gluten free diet
Anti-TTG (negative<9 U/mL, Positive>16U/mL)	>100	47 (01/2017)	8
Fecal calprotectin (normal<50 ug/g, Elevated>200 ug/g)	1450	86	NA
Serum Protein Electrophoresis	Polyclonal hypergammaglobulinemia pattern	Polyclonal hypergammaglobulinemia pattern	Normal pattern
Total protein (60-80 g/L)	89	80	74
IgG (7-16.2 g/L)	21.24	18.58	13.73
C- reactive protein (0-10 mg/L)	<0.3	NA	NA
Ferritin (50-300 µg/L)	15	30	93
ANA	1:160	Negative (01/2017)	1:80
ALT (5-40- U/L)	22	15	13

anti-TTG: anti-transglutaminase antibody

disease and type 1 diabetes, there are reports of CD coexisting with systemic lupus erythematosus and Sjogren's (2, 3). However, the correlation between systemic inflammatory markers and CD has only been described sporadically. Two case reports have reported the presence of hypergammaglobulinemia in patients with CD. The first study reported the case of a patient with autoimmune hepatitis and hypergammaglobulinemic purpura, which are conditions that are confounders of this finding (4); the second case involved an adult with Down syndrome and macroamylasemia (5). In the latter case, hypergammaglobulinemia responded to a gluten-free diet.

Fecal calprotectin is a biomarker of intestinal inflammation that has been studied predominantly in IBD and correlates with the endoscopic disease severity (6). Elevated fecal calprotectin levels are also variably associated with CD. However, two observational studies in an adult CD population were unable to show a difference in fecal calprotectin levels or a correlation with the endoscopic disease severity between the CD patients and the general population (7, 8). However, another study in a pediatric population found significant elevations in the fecal calprotectin results of children with CD compared with the healthy controls, which was similar to our patient. Moreover, calprotectin levels appeared to correlate with the endoscopic lesion severity and responded to a gluten-free diet (9-11). Finally, two prospective studies aimed at determining the diagnostic accuracy of using fecal calprotectin for distinguishing organic versus functional diarrhea found that CD was associated with elevated fecal calprotectin in approximately half of the cases (12, 13). One of the limitations of these data is the use of different cut-offs for fecal calprotectin elevation between the studies. In fact, the cut-off to detect CD might be significantly different from that of IBD.

Currently, the status of CD as a true inflammatory disorder remains unresolved in the literature. There is evidence that CD manifests inflammatory features, at least in a subset of patients, as was the case with our patient, and these features could indicate the potential for diagnosing CD. Thus, we suggest that CD be should be considered during the differential diagnosis of adults with unexplained systemic markers of inflammation and gut inflammation as detected by fecal calprotectin.

Informed Consent: Informed consent was obtained from the patient who participated in this study.

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