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Case Report

Association of Crohn's Disease and Celiac Disease: Causal link or only coincidence?

Tolga Duzenli[1], Mustafa Kaplan[2], Alpaslan Tanoglu[1], Demet Altun[3], Hakan Cermik[4]

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Abstract

Crohn's disease (CD) is a chronic inflammatory bowel disease that affects any part of the gastrointestinal tract, most commonly terminal ileum and proximal colon; and Celiac Disease (CeD) is immuno-mediated systemic disease caused by gluten and similar prolamins in genetically susceptible individuals. Concomitant occurrence of CD and CeD is rare and there are limited literature data regarding the association of CeD to CD. Although, recent findings propose shared mechanisms, genetics and functional pathways. Herein, we report a case that has co-occurrence of CD and CeD and rewiew the literature of the association between these two diseases.

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease that affects any part of the gastrointestinal tract, most commonly terminal ileum and proximal colon. The CD pathogenesis has not been entirely illustrated, but currently it is presumed that the disease is a result of improper immune response to intestinal microflora in genetically susceptible individuals (1).

Celiac Disease (CeD) is immuno-mediated systemic disease caused by gluten and similar prolamins in genetically susceptible individuals (2). CeD can manifest with classical presentation or with atypical symptoms, or even patients may be asymptomatic. Celiac disease affects up to 1% of the North American population (3). A similar prevalence probably exists worldwide. Its manifestations can be variable and usually resemble CD with symptoms of diarrhea, abdominal pain, and iron deficiency anemia (4).

CD has a lower prevalence with values ranging from 26 to 199 per 100000 individuals (5). The prevalence is higher in developed countries and urban areas. A recent increase in the prevalence of both CeD and CD has been reported as a result of several factors (6,7). One of these factors in CeD is the improvement of diagnostic tools (8). CD affects both sexes similarly and the highest incidence is between the second and the fourth decade of life. CeD reveals to be more frequent in women (9), and yet this depends on the age at onset (10). CeD can be diagnosed at any age, but it appears more frequently during childhood (11).

The prevalence of CeD in patients with CD is not clear. There are several cases in the literature describing the coexistence of both diseases in the same family or even in the same patient (12-17). However, some authors contemplate that this is an incidental association and the prevalence of CeD is similar between IBD patients and the general population (18).

Herein, we report a case who has both CD and CeD and rewiew the literature of this association between these two diseases.

Case report

A 24 years-old male referred to our clinic with complaints of nausea, vomiting, abdominal pain, persistent diarrhea and 14 kilograms of weight loss in the last three months. He was hospitalized for further investigations

Author affiliations: *[1]Department of Gastroenterology, GATA Haydarpasa Training Hospital, Istanbul, Turkey, [2]Department of Internal Medicine, GATA Haydarpasa Training Hospital, Istanbul, Turkey, [3]Department of Pediatrics, Etimesgut Military Hospital, Etimesgut, Ankara, [4]Department of Pathology, Etimesgut Military Hospital, Etimesgut, Ankara.*

Correspondence to: *tolgaduzenli@yahoo.com (T.Duzenli)*

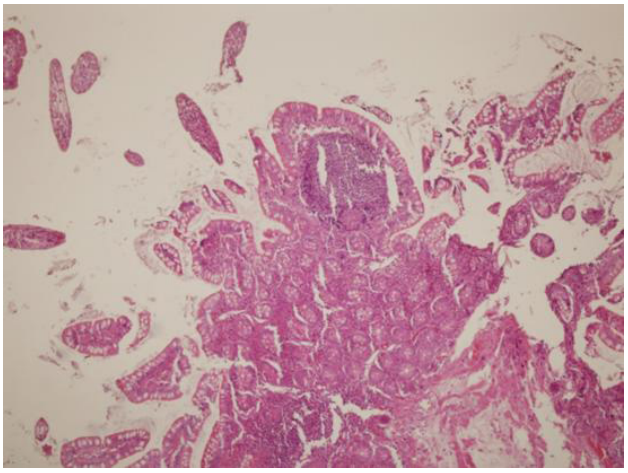

Figure 1. Crohn's disease, ileum, lymphoid follicul in submucosal tissue, dense chronic infiltration. (HE, x40).

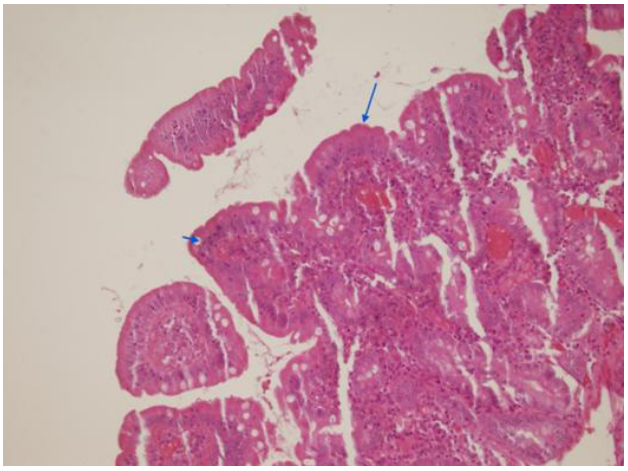

Figure 2. Celiac disease, duodenum, long arrow for villous atrophy; short arrow for increased intraepitelial lymphocytes. (HE, x100).

and an informed consent was obtained. His medical history revealed that the patient was first hospitalized ten years ago in the pediatrics department with similar complaints. He had diagnosed with CD by histological examination of colon biopsies and then received sulfasalazine treatment. The family story was unremarkable. He had tachycardia and paleness of conjuctivae and mucous membranes. Complate blood count demonstrated decreased levels of hemoglobin (8,4 g/dl - reference range: <13,5 g/dL) and mean corpuscular volume (76,9 fL- reference range:<80 fL). White blood cell count was 9810/µL and platelets were 242000/µL. Peripheral blood smear showed hypochromic microcyter erythrocytes and anisocytosis. Routine serum biochemistry analysis and erythrocyte sedimentation rate were normal.

Ileocolonoscopy confirmed the diagnosis of CD. Terminal ileal mucosa was ulcerated with intervals of healthy mucosa, whereas the colonic mucosa appeared macroscopically normal. Histological study of ileal biopsies revealed characteristics of inflammatory bowel disease; abraded and elongated surface epithelium and vertical integration of the crypts, dense polymorphous inflammatory infiltrate in the chorion without crypt abscesses or granulomas and the presence of subacute ileitis with superficial ulceration (Figure 1). Upper digestive endoscopy was performed to rule out the possibility of other underlying diseases like malignancy etc. and to take biopsy. Histological examination of duodenal biopsies showed a nonspecific flat mucosal lesion, villous atrophy and increased number of lymphocytes infiltrating the epithelium compatible with celiac sprue (type 3a according to the classification of Modified Marsh - Figure 2). The antigliadin antibodies immunglobuline A (IgA) and G (IgG) were both positive, as well as the anti-endomysium and anti-tissue transglutaminase antibodies were all positive (IgA and IgG). In our patient, celiac disease was diagnosed years after the onset of and therapy for CD. The diarrhea has stopped following up a gluten-free diet and 7 kg of weight gain has provided within 4 weeks of gluten-free diet. Jejunal rebiopsy documented significant improvement as a mild to moderate villous abnormality. Nowadays, the patient has significant clinical improvement without new complaints.

Discussion

There are very few literature data regarding the association of CeD to CD. Several case reports have described patients with CD or ulcerative colitis refractory to standard therapy, who on further investigation were found to have celiac disease (19-22). Similarly, patients with documented celiac disease have been noted to subsequently receive a diagnosis of inflammatory bowel disease (13,23). Furthermore, two further studies reported high prevalence of inflammatory bowel disease even among the first-degree relatives of patients with CeD (12,24). In Oxford EC et al. s study; while celiac disease is not more common in those with CD or UC, coexisting IBD seems to occur more commonly in patients with celiac disease (25). These observations raise the question as to whether there is truly an association between celiac disease and inflammatory bowel disease.

Immuno-pathogenesis of both CD and CeD have similarities (21). They are related to Th1 pathway characterized by a decreased cellular apoptosis, which provoke a chronic inflammation especially in the lamina

propria (26,27). These findings seem to be related to interleukin-15 (IL-15) action whose over-expression has also been demonstrated (28). Moreover, other cytokines involved in cell-mediated immuno-pathogenesis such as tumor necrosis factor-α (TNF-α), interferon- γ (INF-γ) or interleukin-8 (IL-8) are increased in both diseases (26). All these data confirm the possible common immuno-pathogenesis of both diseases. CD is characterized by an increased gut permeability, which may be related to TNF-α action, and it may provoke a bacterial translocation as consequence of the bacterial overgrowth (29). Increased permeability in CD expose several bacteria mimicking gliadin sequence, and by increasing of cytokines network (IL-15, IL-2, TNF-α, INF-γ), it cause a T Helper (Th1) immunological reaction and development of CeD lesions (30). Also recent literature demonstrates the extensive overlap in the genetic basis of CD and CeD. Genetic studies have identified four shared risk chromosomal loci: PTPN2, IL18RAP, TAGAP, and PUS10 in both diseases (31). This noticeable overlap between the associated genetic regions might indicate partial agreement of the pathogenesis both of these diseases. Patients with IBD and CeD have number of common symptoms like malabsorption, diarrhea, weight loss, loss of BMD and long-standing history of iron deficiency anaemia, and this could cause problems in the diagnostics (32-34).

On the other hand, CD patients have similar mucosal antigenic activation while CeD patients develop none. Furthermore, Human Leukocyte Antigen (HLA) susceptibility of these diseases reveals discrepancy (27). There is a firm relation between CeD and HLA-DQ2 and HLA-DQ8 (35), yet CD and HLA genes seems to have none (34,35).

Several patients affected by CD and CeD are seronegative for anti-gliadin antibodies, anti-endomysial antibodies and anti-tissue transglutaminase antibody. This is particularly true for patients showing slight/moderate histological damage of duodenum (Marsh II-IIIa lesions) (31,32). But, in our case serological tests for CeD were positive, although the patient had Marsh IIIa lesions.

In conclusion, CD may show a correlation with CeD. We think that CeD should be always investigated in CD as soon as possible, although currently there is not enough evidence to recommend routine serological screening for CeD in CD patients (19-22). Especially in patients with CD not responding to immunosuppressive or biological treatment, complicated celiac disease should be considered (20-22).

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