

# The Association of Crohn's Disease, Celiac Disease and Selective Ig A Deficiency

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**Abstract** Concomitant occurrence of celiac disease (CeD) and Crohn's disease (CD) is rare and has been reported in several case reports and series. We report a case of a 63-year-old man with proximal CD, CeD and selective immunoglobulin (Ig) A deficiency (SIgAD). The patient was admitted in our Clinic for evaluation of epigastric pain, nausea, vomiting and weight loss (up to 7 kg) appeared in the last 3 months. The imaging findings from abdominal ultrasound and CT enterography raised suspicion of a lymphoproliferative disease of the jejunum. To exclude the development of lymphoma based on long standing untreated atypical CeD, upper endoscopy with biopsies and serological tests were conducted, showing and subtotal villous atrophy and elevated levels of IgG tissue transglutaminase tTG. Histopathology documented CD (A3,L4,B2 according to Montreal's classification).

**Keywords:** *silent celiac disease, selective Ig A deficiency, Crohn's Disease*

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## 1. Introduction

Celiac Disease (CeD) is immuno-mediated systemic disease caused by gluten and similar prolamins in genetically susceptible individuals [1]. The disease may manifest with classic clinical presentation or with atypical symptoms, or even asymptomatic. CeD may be associated with other autoimmune diseases, immunodeficiencies and malignancies.

Selective immunoglobulin (Ig) A deficiency (SIgAD) is the most common primary immunodeficiency worldwide [2]. Patients with SIgAD have 10- to 20-fold increased risk of CeD, and at least 2.6% of patients with CeD have SIgAD [3]. Patients suffering from SIgAD are often not aware of their IgA deficiency which may delay the diagnosis of CeD [4,5,6,7].

Crohn's disease (CD) is a chronic, relapsing inflammatory bowel disease that can affect any part of the gastrointestinal tract, most commonly ileum and colon. The CD pathogenesis has not been fully clarified, but currently it is assumed that the disease is a result of inappropriate immune response to intestinal microflora in genetically susceptible individuals [8].

Concomitant occurrence of CeD and CD is rare and has been reported in several case reports and series [9-15].

## 2. Case Presentation

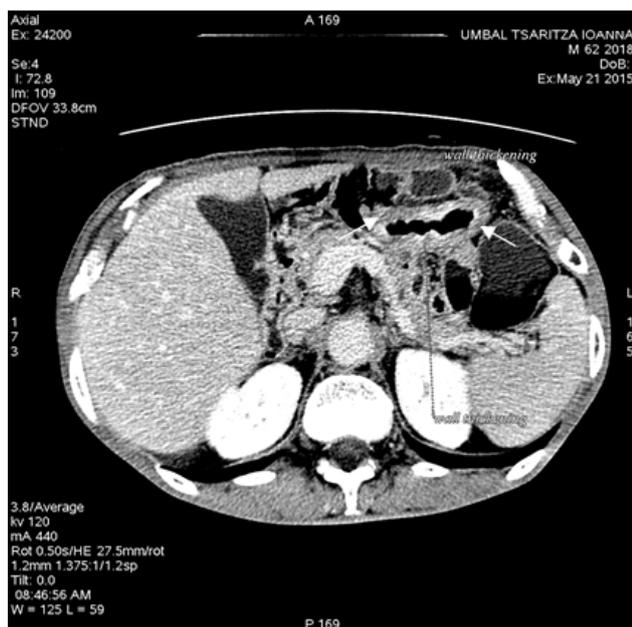
A 63 years old man was admitted in our Clinic for evaluation of epigastric pain, nausea, vomiting and weight

loss (up to 7 kg) appeared in the last 3 months. His bowel habit was regular, without diarrhea or constipation. There was no history of fever, chills, night sweats, hematochezia, or melena. He had no past medical history of taking any medications within the last year. The patient has stopped smoking 3 months ago. He hasn't reported personal or familial history of any oncological or autoimmune diseases. Physical examination at admission revealed only a thin man with pallor of the skin; blood pressure - 130/70 mm Hg, without hepatosplenomegaly or peripheral lymphadenopathy. Initial laboratory tests showed iron deficiency anemia (hemoglobin: 109 g/L [130-180 g/L] ; mean corpuscular volume: 75fl [82-98 fl]; iron: 4.6 µmol/L [6,6-26 µmol/L], C reactive protein: 9.44 mg/dL [0-0.8mg/L], sedimentation rate: 70 mm [up to 30mm/h], albumin: 25 g/L [35-50 g/L], fibrinogen: 569 mg/dL [200-340 mg/dL]. Immunoglobulins serum concentrations showed SIgAD: Immunoglobulin A (Ig A): <0.05 g/L [0.9-3.5 g/L], Immunoglobulin G (Ig G): 13.48 g/L, Immunoglobulin M (Ig M): 2.6 g/L. Serum liver tests, bilirubin and renal function tests were in normal ranges. Stool examinations were negative for intestinal infections and parasitosis. Thyroid function tests and urine analysis were within the normal range. Human Immunodeficiency virus and Mantoux test were negative.

Abdominal ultrasonography showed thickened hypoechoic small bowel wall up to 9 mm (Figure 1). Mild to moderate dilatation of small bowel loops with thickened Kerckring's folds were displayed (Figure 1). It was suspected lymphoproliferative small bowel disease or CD. Colonoscopy was normal up till the terminal ileum with normal ileocolonic histology.



**Figure 1.** Abdominal ultrasound – thickened small bowel wall (up to 9 mm) (white arrows). Small bowel lymphoproliferative disorder was suspected



**Figure 2.** CT enterography - Concentric thickening of the jejunal wall up to 8-9 mm (white arrows)



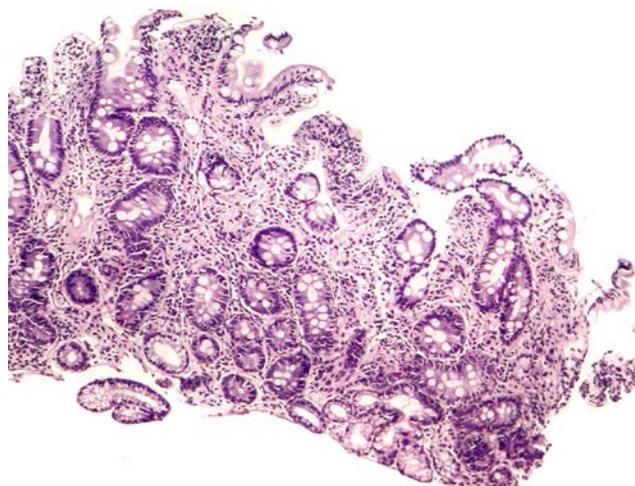
**Figure 3.** CT enterography – Two enlarged mesenteric lymph nodes (white arrows) are shown adjacent to the thickened small bowel wall

CT enterography showed a long segment of at least 30 cm of the jejunum with regular concentric thickened wall

up to 8-9 mm (Figure 2). There was a slight prestenotic dilation. Multiple enlarged mesenteric lymph nodes were discovered (Figure 3). Data suggest firstly small bowel lymphoproliferative disorder.

To exclude the development of lymphoma, based on long standing untreated atypical CeD conventional serological tests and upper endoscopy with biopsies were conducted. Total Ig A serum concentration showed SIgAD. Serological tests for CeD were as follows: Anti tTG Ig A: 0.04 U/ml (normal < 15 U/ml), Anti tTG Ig G: 84 U/ml (normal < 15 U/ml), Anti-gliadin Ig G: 29 U/ml. An upper endoscopy was performed and five duodenal biopsies were taken with two samples from the duodenal bulb.

Duodenal histology showed subtotal villous atrophy of the mucosa, crypt elongation with increased number of intraepithelial lymphocytes, which was consistent with untreated CeD (Marsh–Oberhuber's type IIIb changes) [16,17] (Figure 4).



**Figure 4.** Histology of the duodenal mucosa. Subtotal villous atrophy with crypt hyperplasia and intraepithelial lymphocyte infiltration (x10)

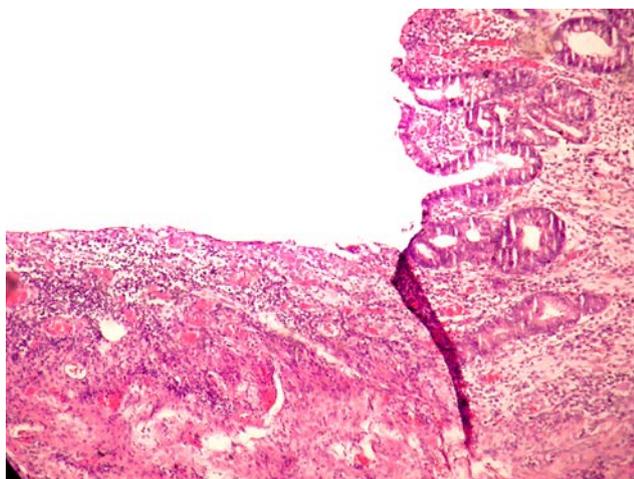
Due to suspicion of enteropathy associated T cell lymphoma (EATL) in association with CeD, as well as the need of histological verification, the patient was referred for exploratory laparotomy. During surgery a stricture in the proximal jejunum about 50 cm distal to the ligament of Treitz and multiple enlarged lymph nodes in the mesenteric area were found (Figure 5). Partial enteric resection with latero-lateral anastomosis was performed. Histological examination of the resected bowel segment showed ulcerated mucosa with inflammatory infiltrates in lamina propria, fibrosis of the submucosa and subserosa (Figure 6). Lymphoproliferative disease was excluded by a normal immunohistochemistry profile of the mucosal lymphocytes without any clonal proliferation. These findings according to the pathologist's opinion were consistent to CD.

The diagnosis of CD (A3, L4, B2 according to Montreal's classification) associated with CeD was established. The patient was prescribed a gluten-free diet and oral azathioprine at a dose of 2.5 mg/Kg/day with iron and vitamin supplements. Nine months of follow-up he presented in a good condition, symptoms-free and reported a weight gain of 6 kg. Hematological and biochemical tests were in normal range and anti tTG Ig G disappeared. HLA tests for CeD or other genetic analysis (incl. NOD2 mutation for CD) were not performed due to

financial reasons as our healthcare insurance fund does not cover the costs of genetic tests.



**Figure 5.** Macroscopic finding of the resected jejunal segment – 50cm long segment with thickened wall and stricture in the proximal region. Wall thickness is up to 1cm



**Figure 6.** Histology of the resected jejunal segment – ulcerated mucosa with inflammatory infiltrates in lamina propria, fibrosis of the submucosa and subserosa

### 3. Discussion

CeD and CD are autoimmune conditions that affect the digestive system and share many symptoms.

CeD is more common in women. CD affects both genders similarly, most often between the second and fourth decade of life. The combination of both diseases is more common in young males. The upper GI tract location of CD is also more often in young patients. Only 10-15% of the cases with CD appear in patients older than 60 years [18]. In the majority of the published cases, CeD preceded the diagnosis of CD [11,12,19]. Furthermore, most patients had symptomatic CeD and colonic or terminal ileum CD [20,21].

Our clinical case was interesting at least for several reasons – association of CeD with CD; the proximal location of CD; the older age of the patient and the presence of SeIgAD

Perhaps the combination of CeD and CD is actually more common. Indeed, Tursi et al. in one prospective

study establish high prevalence of CeD in a consecutive series of patients affected by CD patients (almost 26%) [15]. Probably due to the atypical clinical course in the most of patients sometimes CeD remains undiagnosed. In our case, the detection of the disease is due to the suspicion of small intestine lymphoma, which may be associated with untreated CeD or with CD.

Our patient presented with similar symptoms for both diseases probably after a long subclinical course. Both diseases share an oligosymptomatic mode of presentation with nonspecific overlapping symptoms. The late manifestation of CD may indicate the silent character of CeD as no clinical presentation has been observed for many years. Although both diseases were diagnosed simultaneously, it was unclear which of them had developed earlier. CT enterography findings for jejunal stenosis suggested the longer CD duration. It is not clear why this patient has not had any clinical symptoms for a long time.

The association between CeD and SIgAD complicates serological testing for CeD [7]. Indeed, routine serology of CeD is IgA-based and is expected to be negative in IgA-deficiency as in our patient. Diagnosis of CeD was confirmed by the positive IgG anti tTG antibodies and histological findings of subtotal villous atrophy from multiple duodenal biopsies.

The association of CD and CeD may be explained by shared genetic predisposition, increased gut permeability to antigens observed in both diseases [7,9,10,14,15,20].

The present and similar clinical cases have described in the medical literature raise in testing for CeD in patients with CD, although currently there is not enough evidence to recommend routine serological screening for CeD in CD patients [7,15].

### 4. Conclusion

Our case report is of interest because of a very rare combination of silent CeD, SIgAD and active CD of the

upper gastrointestinal tract with stricturing behavior. Moreover, all these disorders were diagnosed at the same time in 63-year-old man.

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