CASE REPORT

DOI: 10.5336/caserep.2018-63259

Latent Celiac Disease and Undifferentiated Connective Tissue Disease Association

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Received: 11.10.2018
Received in revised form: 03.01.2019
Accepted: 18.02.2019
Available online: 04.03.2019

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ABSTRACT Celiac Disease (CD), is a common autoimmune disorder of the small intestine. Here we present a case in which has Latent Celiac Disease (LCD) and Undifferentiated Connective Tissue Disease (UCTD) association. The patient presented with abdominal pain, constipation, bloating, joint pain and wounds in the mouth as complaint. The patient were detected that iron, vitamin D and B12 deficiency, ANA, Antigliadin Ig G, Tissue transglutaminase IgG and HLA-DQ2 positivity. The clinical, laboratory, and interventional results of the patient were not fully compatible with a specific rheumatic disease pattern. No pathology was detected in the esophagogastroduodenal endoscopy but the gluten-free diet, based on clinical findings, provided clinical improvement. It is known that autoimmune or rheumatologic disorders are more common in celiac patients than in the normal population. We presented this case as a case of UCTD accompanying LCD to bring a different perspective to the pathophysiology of Celiac disease.

Keywords: Celiac disease; undifferentiated connective tissue disease; diet; gluten-free

"Gluten Sensivity (GS)" or "Gluten intolerance" is a clinical term utilized to define indigestion and abnormal immunological activity caused by gluten. GS classified into three categories: Autoimmune Celiac Disease (CD), wheat allergy, and Non-Celiac Gluten Sensitivity (NCGS).[1] The best known and notable form of these disorders is CD. Despite the exact global prevalence is still unknown, global prevalence of CD with positive seroprevalence is estimated to be 1.4% and biopsy-confirmed CD is 0.7% according a meta-analysis published in 2018.[2] There are also studies with a prevalence of CD of 4.8% and a definite diagnosis of 3.2% based on biopsy results. In addition, no significant difference was found in terms of age and gender.[3]

Many subforms of CD have been identified, such as Seronegative CD, Latent or potential CD, Lymphocytic Duodenosis and borderline cases.[4] Numerous types and sub-forms are also an important factors which complicates CD diagnosis. Another obstacle to diagnose is the digestional problems such as diarrhea, gas, bloating, as well as the atypical clinic due to diseases arise from other organ systems.[5] Nearly half of the patients have extraintestinal clinical presentation such as asthenia, fatigue, poor appetite, weight loss, low mental performance and chronic musculoskeletal pain, iron deficiency anemia and other micronutrient deficiencies, dermatitis herpetiformis, osteoporosis, recurrent aphtous stomatitis, infertility, peripheral

neuropathy, arthralgia, artritis and psychiatric diseases.[5-7] Many patients spend their 6 to 10 years without accurate diagnosis for their symptoms due to these uncertainties.[6]

CASE REPORT

A 24-year-old woman who has no chronic or genetic disease, had been examined in outpatient clinic because of recurrent oral aphtous ulcers, dispeptic symptoms and occasionally swelling and several joint pains. In addition, the patient claimed to see a dietitian because she gained 10 kilograms in last year.

She did not have any gastrointestinal or extraintestinal symptoms until age 18. She has often experienced oral aphtous lesions since her childhood. She had occasionally symptoms which are usually constipation, meteorism, abdominal discomfort and distension and rarely diarrhea. Eight months ago, she had been examined in the Internal Medicine Outpatient Clinic because of wide and deep aphtous lesions in her oral mucosa. Due to her initial examination and hematological test results [high level inflammatory markers and positive homogeneous pattern of Anti nuclear antibody (ANA)] the patient was considered to have Behçet's Disease (BD) by internal medicine specialist. Therefore, Pathergy test was applied and the patient consulted to Ophtalmology Clinic and BD was ruled out. Local treatment for oral aphthae was prescribed and redirected to follow-up in outpatient clinic. According to her expressions, a few months ago, she had slight pain and swelling on her right wrist for a week. But her symptoms healed spontaneously without any medical treatment.

The patient finally came to the Family Medicine outpatient clinic with symptoms such as weight gain, fatigue and abdominal distention. After a detailed investigation, it was learned that she had intestinal irregularity, bloating, gas, constipation, indigestion complaints especially over consumption of pastry and bread. She had no significant family history. The results of her physical examination as follows: Her vital signs were stable. There was a small oral lesion but she did not complain about having oral aphthaes due to the fact that the patient got used to live with them unless they were very large. Upper extremity joints especially the joints on right limb were sensitive, but there were no swelling or redness. She had no genital ulcers. Other systematic examinations were normal. Her lenght:160 cm, weight:70 kgs. BMI: 27,34 kg/m^2. Routine blood parameters are summarised on Table 1.

There was a previous joint swelling and sensivity story with oral aphthous lesion, therefore we consulted the patient to Rheumatology Clinic in order to investigate a rheumatic or connective tissue disease. Although ASO and RF tests were found

TABLE 1: Laboratory test results of the patient.

Parameter	First visit	3 months after
Glucose (mg/dL)	87	80
Creatinin (mg/dL)	0.9	0.77
AST(U/L)	18	18
ALT(U/L)	13	14
GGT(U/L)	13	
LDH(U/L)	172	
ALP(U/L)	62	
Total Bilirubin	0.52	
D.Bilirubin (mg/dL)	0.11	
Uric acid (mg/dL)	4.57	
Calcium (mg/dL)	9.33	
LDL cholesterol (mg/dL)		77
HDL cholesterol (mg/dL)		55
Cortisole (µg/dL)	6.12	
Folic acid (ng/mL)	12	
Vitamin B12 (pg/mL)	**97**	138
TSH (IU/mL)	0.54	1.09
Ferritin (ng/ml)	**15**	49.5
Vitamin D (ng/ml)	**8.94**	38.5
WBC (10^3/µL)	5700	6400
Hb (g/dL)	13.4	13.7
Platelet (10^3/µL)	263000	286000
Sedimentation (mm/h)	**37**	7
CRP (mg/L)	**35.4**	2.6
RF (IU/ml)	<20	
C3c (g/L)	1.16	
C4 (g/L)	0.22	
Anti HBs	Negative	
Anti HIV		
Anti HCV		
Urine analysis	Normal	

to be normal, ANA resulted in (++ homogeneous pattern), tissue transglutaminase and antigliadin antibodies (AGA) resulted in positive. The patient had no previous food allergy story, including wheat. After further autoimmune blood tests (the outcomes were summarized in Table 2, she had been diagnosed with "Undifferential Collagen Tissue Disease" and prescribed Hydroxychloroquine sulfate 200 mg twice a day after an ophtalmologist consultation. She had no active joint inflamation so cortisone therapy did not prescribed. Also, her genetic profile related to CD was reported HLA DRQ2 positive and HLA DQ8 negative. Because of the posivity of ANA, tissue transglutaminase and AGA; esophagogastroduodenoscopic diagnostic biopsy had been done. There was no significant result in macroscopic examine but antral gastrit. Microscopic pathologyc examine was reported as "*Helicobacter pylori* (-), intestinal metaplasia (-)". Also abdominal ultrasonography was reported normally. Cyanocobalamin and Vitamin D replacement treatment were performed and the patient was consulted to a nutritionist to recommend a gluten-free diet (GFD) to treat the intestinal symptoms. Patient had gone on gluten-free diet and she had been recommended for control examine one month later. When she came to her appoinment, her digestive symptoms were diminished and she was smiling. During the six months follow up period after initiating GFD, she has been symptom-free and she has been receiving no medical treatment accept continuing diet.

TABLE 2: Autoimmune antibody results of the patient.

Autoimmune antibody levels		
Tissue transglutaminase IgM	2.79	(Negative)
Tissue transglutaminase IgG	23.8	(Positive)
Anti Gliadin IgG	5.1	(Negative)
Anti Gliadin IgA	38.3	(Positive)
Anti beta-2 glikoprotein IgM	1.13	(Negative)
Anti beta-2 glikoprotein IgG	0.94	(Negative)
Anti cardiolipin		(Negative)
Anti fosfolipid		(Negative)
Anti-SSA		(Negative)
Anti Sm D1		(Negative)
Anti -SSB		(Negative)
Anti-Sm-RNP		(Negative)
ds DNA		(Negative)
Anti-Jo1		**(intermediate value)**
Anti-Scl 70		(Negative)
Anti nuclear antibody (ANA) 1/320-1/1000		**(++ homogeneous patern)**

Informed consent was obtained for using, writing and publication of her medical information from patient.

DISCUSSION

The present case report demostrates that a Latent Celiac Disease accompanied by Undifferential Collagen Tissue Disease. It is an atipical celiac case to improve our perspective to understand the associated pathophysiology.

CD is common not only in the pediatric population but also in adults. If patients with nonspecific symtoms have been questioned indetail, these symptoms will become known that they proceed since childhood.[5] In contrast, the frequency of increased atypical CD clinical conditions, including anemia and osteoporosis, arises as the use of serological tests.[8] Investigation of relatives of a celiac patient is important for preventive medicine.

Abdominal discomfort and bloating which is one of the most common symptoms of CD, often leads to a false diagnosis of irritable bowel syndrome (IBS).[5] The patient neglected abdominal distension and concomitant constipation for years, and those symptoms were recurrently caused that physicians could not give effective treatment because of considering dyspepsia or IBS. Positive serology and/or histology are used to diagnose CD.[6] The genetic influence in the pathogenesis is based on the familial transition and the presence of alleles encoding HLA-DQ2 in some cases and HLA-DQ8 proteins in most cases.[8,9]

Wheat allergy should be questioned among the differential diagnoses of the disease; In our patient neither wheat, oat or rye allergy was detected in childhood or adulthood.[10] In addition to the presence of symptoms in our patient, serological tests were positive, biopsy reported negative and genetic tests reported positive. Although all of

these findings indicated CD, patient had a latent clinical progress. The positive serology allowed us to exclude NCGS. The patient had no skin rash or acute diarrhea after gluten consumption at the time she consulted to us. She had been complaining of abdominal swelling after intense gluten supplementation but it was neglected because of the bias that she might have Behçet's disease. As in the literature, non-erosive arthritis, normal ocular tests with normal salivary gland biopsy despite findings suggestive of Sjögren Syndrome, and ANA and Anti-Jo-1 (intermediate) positivity as in our patient were found in favor of early UCTD. In follow-up, the rheumatologic diagnosis of the patient may proceed in different directions. Despite the proven benefits of a gluten-free diet, it is extremely difficult to avoid gluten-containing foods completely, and compliance with the diet is thought to be between 45% and 80%.[6,8]

Even though it took time for our patient to adapt to the removal of gluten from her diet, she continued for a while because it had a beneficial effect on her symptoms. However, we learned that the patient occasionally disrupts her diet due to decrease in her life quality. This reveals that there is a certain requirement for easier and suitable treatment alternatives for CD indeed. This case indicates that in patients who have multiple symptoms esp., digestive symptoms for years, gluten sensitivity should not be disregarded and at least the simple antibody blood tests should run if there is a clinical suspicion.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Özlem Güç Suvak;* ***Design:*** *Özlem Güç Suvak;* ***Control/Supervision:*** *Cenk Aypak;* ***Data Collection and/or Processing:*** *Özlem Güç Suvak;* ***Analysis and/or Interpretation:*** *Özlem Güç Suvak;* ***Literature Review:*** *Özlem Güç Suvak;* ***Writing the Article:*** *Özlem Güç Suvak;* ***Critical Review:*** *Süleyman Görpelioğlu;* ***References and Fundings:*** *Özlem Güç Suvak,Cenk Aypak, Süleyman Görpelioğlu;* ***Materials:*** *Özlem Güç Suvak.*

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