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RESEARCH ARTICLE

A disease to consider in the differential diagnosis of lower back pain: Celiac disease and related autoimmune disorders

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Abstract

Introductıon: Celiac disease (CD) is an autoimmune disease caused by gluten ingestion in genetically susceptible individuals. Although gastrointestinal system symptoms are common, extraintestinal symptoms may be seen during the disease course. Due to similar genetic features and pathogenetic pathways for autoimmunity, increasing rheumatological diseases have been reported in CD in recent years. In this study, we aimed to evaluate patients with CD in terms of musculoskeletal symptomatology and presence of rheumatic disease and autoantibody positivity.

Methods: The study was designed as a cross-sectional, retrospective cohort study. Between January 2020-2022, 65 patients with CD who were followed-up in the gastroenterology clinic of our hospital and consulted to the rheumatology outpatient clinic for any reason were included in the study. Medical records were reviewed, laboratory and imaging results were recorded.

Results: Admission to the rheumatology clinic, the most common symptoms were inflammatory back pain(IBP) (43.1%) followed by xerophthalmia (15.4%). None of the patients with IBP had radiographically active sacroiliitis. In total, concomitant rheumatological diseases were 6 (9.2%): 2 patients (3.1%) had Sjögren's syndrome and one undifferentiated connective tissue disease, systemic lupus erythematosus, psoriatic arthritis and familial Mediterranean fever. Except for the CD autoantibodies, the frequency of anti-nuclear antibodies (ANA) was 38%, and the most common extractable nuclear antigen (ENA) patterns were DFS-70 and SSA.

Conclusion: Although the most common symptom is IBP, the absence of radiographic findings of spondyloarthritis in CD patients suggests these to be a non-rheumatological cause associated with CD. On the other hand, CD patients with xerophthalmia and/or ANA positivity may need to be evaluated for connective tissue diseases, especially SjS.

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Introduction

Celiac disease (CD) is a chronic autoimmune disease with multisystem involvement that arises due to gluten intake in genetically predisposed individuals. Its prevalence in the general population is around 1%.[1] The common symptoms of the disease are directly associated with the gastrointestinal system (GIS). GIS symptoms include diarrhea, loss of appetite, abdominal bloating, and failure to thrive, and they are more commonly observed in the pediatric population.[2] Less frequently, CD can also manifest with a systemic course with extraintestinal symptoms. Extraintestinal symptoms are common in both children and adults.[2] In 40% of cases, microcytic anemia due to iron deficiency [3] (caused by malabsorption of iron or chronic inflammation) or, more rarely, macrocytic anemia due to folate and/or B12 vitamin deficiency can be observed. Changes in the absorption of calcium and vitamin D3 are associated with osteopenia and osteoporosis.[4]

Gluten is a commonly used term for the insoluble protein complex derived from wheat, rye and barley.[5] It is poorly digested in the human intestine. Gluten peptides pass through the submucosa of the small intestine without being fully broken down. In genetically susceptible individuals (90-95% HLA, the remaining portion HLA-DQ8), this leads to the development of an immune (anti-deamidated gliadin antibodies - DGP) and autoimmune (anti-endomysial antibodies - EMA, anti-tissue transglutaminase antibodies - tTG) reaction. In patients, the adaptive immune system is more dominant, leading to the production of anti-EMA and anti-tTG antibodies, lymphocytic infiltration in the intestinal mucosa, and destruction of villus architecture.[6]

The increased prevalence of autoimmunity and rheumatic diseases in CD can be explained by shared genetic characteristics, common triggers, or compromised intestinal permeability. Similar to CD, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients have been found to exhibit mild inflammation in the small intestinal mucosa along with an increased number of intraepithelial lymphocytes (IELs).[7] On the other hand, symptoms related to joint and muscle involvement have been described in individuals with CD.[8] In conclusion, while initially considered a homogeneous disease, it is now acknowledged that CD encompasses a broader clinical spectrum. The relative risk of associating one or more autoimmune pathologies is approximately three times higher in individuals with CD compared to the general population.[9] Furthermore, about 30% of CD patients also have another accompanying immune pathology.[10] In recent years, systemic involvement in CD has been studied further, and musculoskeletal symptoms have also been described. In a study conducted by Jericho et al,[11] a significant number of adult patients exhibited musculoskeletal symptoms: arthralgia (16%), arthritis (15%), and myalgia (8%). Similarly, various studies have suggested associations between CD and back pain, sacroiliitis,[12] RA, SLE, vasculitis, polymyositis, and CD.[13] However, there are different results in the literature as well. A different study conducted by Shor et al.[14] İndicated that among the frequently detected autoantibodies in CD, anti-gliadin immunoglobulin G (IgG) antibodies were only observed in 12 out of 186 patients with RA. Similarly, another study has reported that RA is observed in CD patients at a lower rate compared to controls.[15]

Due to the conflicting results in the literature, more research is needed on this topic. So, in this study, we aimed to evaluate patients with CD in terms of rheumatological symptomatology and presence of rheumatological disease and autoantibody positivity.

Material and Methods

Study design

This study was designed as a cross-sectional, retrospective cohort study with approval by Ankara City Hospital ethics committee dated 07/09/2022, numbered E1-22-2862 and was therefore performed in accordance with the ethical standarts laid down in the 1964 Declaration of Helsinki and its later amendments. The study included patients who were under follow-up at the Gastroenterology Clinic of Ankara City Hospital with a diagnosis of CD and had sought care at the Rheumatology outpatient clinic for any complaints. For this purpose, the patients' medical records were reviewed. Additionally, patients were contacted or their information was gathered when they attended follow-up outpatient appointments.

Main outcomes and other variables

Demographic characteristics, medical treatments, laboratory and imaging results were also collected from the hospital database. Musculoskeletal complaints of the patients, rheumatological diseases and other comorbidities were also recorded separately. All evaluated autoantibodies of the patients were recorded. Except for celiac disease-related au-

toantibodies, antinuclear antibodies (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) and extractable nuclear antigen (ENA), which are used in the diagnosis of rheumatologic diseases, were recorded. Laboratory upper limits for antibodies used in the diagnosis of rheumatological diseases were considered positive as follows: ANA >1/100 U/mL, RF >20 IU/mL , anti-CCP>5 U/mL. Antibody titers were indicated in patients with ANA positivity. If there is any subgroup antibody positivity in the ENA test, the ENA test was considered positive and the subgroup antibody was also specified. MEFV and HLA-B27 genetic test results performed in patients deemed necessary according to rheumatological symptomatology were also recorded.

Statistical analysis

Data are analyzed using Statistical Package for the Social Sciences (SPSS) 22.0 software (SPSS.Inc., Chicago, IL). Normality of continuous variables is evaluated with Shapiro–Wilk test and with plots and histograms visually. Continuous variables are presented either with median (minimum–maximum, min-max) or mean±standard deviation, according to normality. Categorical variables are presented with numbers and percentages.

Results

Our study included 65 patients who were under follow-up in the gastroenterology clinic with a diagnosis of CD. Forty-seven patients (72.3%) were female and the median age of these patients was 31 years (min-max: 18-70). The demographics features and comorbidities of CD patients are presented in Table 1. The median duration of diagnosis for the patients was 3 years (min-max: 0-20). In CD related autoantibodies, the most frequently detected autoantibody was anti-tissue transglutaminase IgA (64.6%), followed by anti-endomysial IgA (53.8%), and anti-gliadin IgA (40%). Interestingly, 21.5% (n=14) patients had negative CD related autoantibodies; they were diagnosed with CD according to endoscopic biopsy.

The most common rheumatological complaint was inflammatory back pain (43.1%, n=28), followed by dry eyes (xerophthalmia) in 10 patients (15.4%), hip pain in 8 patients (12.3%), and oral ulcers (aft) in 8 patients (12.3%). Among patients describing inflammatory back pain, direct radiographs were evaluated and an enthesitis-like appearance was observed in 7 patients (10.5%). Similarly, irregularities and grade 1 sacroiliitis were found in 7 patients (10.5%) on sacroiliac direct radiographs. Eight patients underwent magnetic resonance imaging (MRI), but none of them showed active sacroiliitis.

Table 1. Demographic and clinical characteristics of patients followed up with celiac disease

Age, year, meadian (min-max)	31 (18-70)
Female, n (%)	47 (72.3)
Comorbidities, n (%)	
Autoimmune hypothyroidism	7 (10.8)
Diabetes mellitus	4 (6.2)
Sjogren's syndrome	2 (3.1)
Undifferentiated connective tissue disease	1 (1.5)
Systemic lupus erythematosus	1 (1.5)
Psoriatic arthritis	1 (1.5)
Familial Mediterrean fever	1 (1.5)
Disease duration, year, median (min – max)	3 (0-20)
Reasons for referral to rheumatology clinic, n (%)	
Inflammatory back pain	28 (43.1)
Xerophtalmia	10 (15.4)
Hip pain	8 (12.3)
Oral aphthae	8 (12.3)

In the evaluation of concomitant rheumatological diseases, Sjögren's syndrome (SjS) was present in 2 patients (3.1%), undifferentiated connective tissue disease (UCTD) in 1 patient (1.5%), systemic lupus erythematosus (SLE) in 1 patient (1.5%), psoriatic arthritis (PsA) in 1 patient (1.5%), and familial Mediterranean fever (FMF) in 1 patient (1.5%). The most common non-rheumatological comorbidity accompanying CD was autoimmune hypothyroidism, which was present in 7 patients (10.8%), followed by DM in 4 patients (6.2%). Among these 4 DM patients, 3 (75%) were being followed up for type 1 DM.

Antibodies associated with rheumatological diseases are presented in Table 2. RF positivity was detected in 2 patients (3.1%). In these patients, the positivity was at a low titer (>20 IU but <60 IU) (1st patient RF: 19, 2nd patient RF: 36). Anti-CCP positivity was observed in only 1 patient. ANA positivity was more common, found in 25 patients (38.5%). Among these patients, ANA titers were 1/100 in 15 patients (23.1%), 1/320 in 7 patients (10.8%), while the remaining 3 patients showed higher titers of ANA positivity (1/1000-1/3200). In the ENA tests, dense fine speckled (DFS) positivity was observed most frequently (6 patients, 9.2%). Additionally, an-

ti-SSA positivity was detected in 4 patients (6.1%). Other autoantibodies with positive findings were anti-SSB, anti-Ro52, anti-Mi2, anti-Ku, anti-Scl70, and anti-histone antibodies. Genetic mutation analysis for Familial Mediterranean Fever (FMF) was conducted on 7 patients. Among these patients, 1 (14.2%) had the M694V heterozygous mutation, 1 (14.2%) had the E148Q heterozygous mutation, and in the other 5 patients (71.4%), no mutation was detected. Genetic analysis for HLA-B27 was performed on 7 patients. Among the tested patients, 1 (14.2%) was positive, and the remaining 6 (85.8%) were negative for HLA-B27.

Table 2. Commonly Detected Autoantibodies Positivity in Patients Followed with Celiac Disease

RF, n (%)	2 (3.1)
Anti-CCP, n (%)	1 (1.5)
ANA, n (%)	25(38.5)
1/100	15 (23.1)
1/320	7 (10.8)
1/1000-1/3200	3 (4.5)
ENA, (%)	
DFS	6 (9.2)
SS-A	4 (6.1)

Discussion

With improved diagnostic methods and comprehensive screening of individuals considered at risk, Celiac disease has seen a significant increase in prevalence over the past 50 years.[16] In Western countries, the prevalence of histologically confirmed CD patients is around 0.6%, while the prevalence of serological screening in the general population is approximately 1%. The female-to-male ratio varies between 1:3 and 1.5:1. The disease is known to affect all age groups, with over 70% of patients being diagnosed after the age of 20.[17] CD may present with a variety of different symptomatology. Traditionally, patients present with symptoms like diarrhea, steatorrhea, and weight loss. However, CD can manifest with a wide range of symptoms and findings including anemia, reflux esophagitis, eosinophilic esophagitis, neuropathy, ataxia, depression, short stature, osteomalacia, osteoporosis, and unexplained elevated liver transaminases.[11,13,18,19] Gluten is a significant trigger factor in CD. The term "gluten" refers to a mixture of proteins from wheat, including gliadin and glutenin, as well as similar proteins from other grains.[20] Prolamins, a complex group of alcohol-soluble lectins, constitute important seed proteins in grains. The most abundant gluten prolamins (gliadin and glutenin) are primarily found in wheat. However, other grains such as barley (known as hordeins), rye (secalins) and oats (avenins) also contain substantial amounts of prolamins.[21] The pathophysiology of CD arises from a complex interplay between genetic and environmental factors that lead to an inappropriate immune response in affected individuals.

Gluten may trigger other autoimmune processes beyond CD. In a study, it was demonstrated that gluten has effects on spontaneous autoimmunity in non-obese diabetic mice.[22] When exposed to dietary gluten, these mice exhibit high levels of mucosal proinflammatory cytokines and develop minor intestinal enteropathy. The abnormal immunological response triggered by proteins derived from gluten can lead to the production of different antibodies affecting various systems. Most commonly, in CD, antibodies are produced against members of the transglutaminase (TG) family, particularly IgA-class antibodies targeting transglutaminase 2 (TG, also known as protein-glutamine γ-glutamyltransferase),[23] in dermatitis herpetiformis against TG2 and TG3, and in gluten ataxia against TG6.[24]

There are two significant questions in the relationship between CD and autoimmunity. First, "does CD directly lead to other autoimmune diseases?", second, "can the clinical course of autoimmunity be altered in CD patients by adopting a gluten-free diet?". There are various studies in the literature addressing these questions. For instance, there are numerous studies regarding the relationship between CD and RA, one of the most common rheumatological diseases.[25,26] In those studies, there can be conflicting results regarding the prevalence of CD in patients with RA. For instance, in a study by Elhami et al,[27] the estimated rate of CD among RA patients is approximately 3%, which is three times higher than the healthy population. However, in another study, a lower association between RA and CD was found compared to control groups.[28] In our study, we did not observe any cases of RA in individuals with CD. When considering the other results of our study, we found a frequency of 3.1% for SjS among individuals with CD. According to the 2020 European League Against

Rheumatism (EULAR) SjS guidelines, the prevalence in European countries ranges from 1 to 23 individuals per 10,000 people (0.01% - 0.23%).[29] When comparing these frequencies, our study suggests a higher prevalence of SjS in individuals with CD.

The literature has demonstrated through various studies that extraintestinal manifestations are frequently observed in CD.[30,31] Rheumatological symptoms are frequently encountered in CD patients, mainly musculoskeletal symptoms. Myalgia, a common symptom of CD, can be associated with nutritional deficiencies or systemic inflammation.[11] Arthralgia and arthritis, which are reported to occur in approximately 20-30% of cases, are also common musculoskeletal symptoms.[32] In patients with CD, excessive vitamin D and calcium malabsorption due to villous atrophy leads to secondary hyperparathyroidism, dramatic decrease in bone mineralization, and osteomalacia.[33] This condition is one of the important causes of arthralgia and myalgia seen in patients. In our study, similar to the data in the literature, musculoskeletal symptoms were quite common in CD. A recent meta-analysis, despite an increase in the frequency of arthralgia, indicated that the frequency of arthritis does not increase in CD.[32] Our study also found that the frequency of inflammatory arthritis did not increase. Xerophthalmia, the second most common extraintestinal complaint in our study, is also commonly seen in CD, consistent with the literature. The prevalence of SjS in CD varies between 1% and 14.7% in various studies.[34,35]

Our study has certain limitations. The most important limitation is the relatively small number of CD patients. Another significant limitation is the retrospective nature of our study. Evaluating patients based on their presenting complaints and conducting assessments and investigations prospectively might yield different results.

Conclusion

In our study, rheumatological symptoms, especially musculoskeletal symptoms, were quite common in patients with CD. Although IBP is the most common rheumatological symptom in CD, we did not find evidence of spondyloarthritis confirmed by radiological imaging. Xerophthalmia was the second most common rheumatologic symptom and an increased prevalence of SjS was found similar to some studies in the literature. According to our findings, CD patients with xerophthalmia and/or ANA positivity may need to be evaluated for connective tissue diseases, especially SjS. However, larger and more comprehensive studies are needed to better show the relationship between rheumatological diseases and CD.

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Conflicts of interest:

The authors declare no conflicts of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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