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ORIGINAL ARTICLE

Clinical profile of patients with seronegative celiac disease

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ABSTRACT

Aim: This study aimed to determine the clinical profile of patients with seronegative celiac disease (SNCD).

Background: Celiac disease (CD) is mainly diagnosed based on positive serology and duodenal mucosal atrophy, but some patients have negative serology. Their diagnosis has some limitations; delays in diagnosis are likely accompanied by a poor prognosis and a high risk of developing complications of CD.

Methods: In this retrospective study, 1115 patients were evaluated for CD with mucosal atrophy between 2010 to 2020. SNCD diagnosis requires genetic CD predisposition and improvement of both clinical symptoms and regrowth of duodenal villi after 12 months of a gluten-free diet (GFD) for all patients with IgA deficiency, other IgG-based serology for diagnosis of celiac was done and if these antibodies were negative, consider them as possible SNCD. If they had positive DQ2-DQ8 and improvement of clinical symptoms and mucosal atrophy after 12 months of GFD were confirmed SNCD.

Results: Of the 1115 study subjects, 27 had SNCD, 1088 had SPCD with a mean age of 29.7±15.7 years (1 to 76 years) in seropositive celiac disease (SPCD) subjects and 37.1±16.3 years (6 to 63 years) in SNCD participants and 19 female patients with SNCD were presented. The BMI of SNCD and SPCD patients were reported 23.9 and 21.4, respectively. In addition, SPCD subjects were more likely but not statistically significant to have a positive family history. Villous atrophy was shown in 100% SNCD and 95.6% SPCD cases. Scalloping and fissuring in duodenal biopsies were reported in 60% of SNCD and 84.5% of SPCD patients. There was some other cause of seronegative villous atrophy including 3 patients with Crohns disease, 2 with common variable immunodeficiency, 2 drug and one patient with peptic duodenitis. Anemia, neurological symptoms, and liver function tests (LFT) abnormality were common extra intestinal manifestations in SNCD individuals. Levels of Thyroid peroxidase (TPO), TSH were measured, it had been detected that SNCD cases had a higher rate of co-occurrence with thyroid diseases also SPCD cases showed a higher rate of co-occurrence with diabetes.

Conclusion: Among patients with celiac disease 2.4% are SNCD. SNCD are older than SPCD at the time of diagnosis and have higher BMI. Most common of cause of seronegative enteropathy also is SNCD followed by inflammatory bowel disease (IBD) common variable immunodeficiency (CVID), medication use, and duodenitis, in this area.

Keywords: Clinical profile, Seronegative celiac disease.

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Introduction

Celiac disease (CD) is a common inflammatory illness involving the immune system induced by gluten

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consumption (1). In patients with Celiac diseases, an immune response to gliadin culminates in villous atrophy and lymphocyte infiltration of the lamina propria and epithelium (2). According to serological research, the prevalence is roughly 1% in the majority of areas (3). CD is a disease that affects people of all ages (4).

Clinical symptoms of CD are classified as gastrointestinal or extraintestinal symptoms (5). Gastrointestinal manifestations are frequently characterized by classic symptoms such as diarrhea, weight loss, abdominal pain, and malabsorption (6). Extraintestinal manifestations include mucocutaneous (such as herpetiform dermatitis (7, 8)), metabolic bone diseases (osteomalacia, osteoporosis, hematologic (iron deficiency anemia), and neuropsychiatric disorders mostly including peripheral neuropathy, anxiety, depression, and gluten ataxia (9, 10)). Adults are diagnosed with tissue transglutaminase (tTG)-IgA antibody and duodenal biopsy, which demonstrates mucosal atrophy, before commencing a Gluten-Free Diet (GFD) (1, 11).

IgA deficiency is particularly prevalent in celiac patients, furthermore, patients with selective IgA deficiency showed a high prevalence of CD (11) due to the high prevalence of CD in patients with IgA deficiency, the diagnostic CD path must include both TGA IgA and total IgA levels and all patients should have their TGA IgA and total IgA levels measures. If patients are IgA deficient, an IgG-based test using deaminated gliadin peptide (DGP)-IgG or TGA- IgG should be conducted (11). Most CD diagnoses are based on clinical, serological, histological, and occasionally genetic findings (1). However, CD antibodies may be negative in a subset of CD patients, resulting in creating a new diagnosis called seronegative celiac disease (SNCD) (1).

SNCD has been reported to occur in 6.4-9.1% of the total number of celiac patients (12). Diagnostic criteria are the findings of villous atrophy, the negativity of TGA, IgA, normal IgA total and positive genetic markers (HLA-DQ2 and/or -DQ8). Additionally, to confirm the diagnosis, improvement in histology and clinical symptoms must be demonstrated after a GFD period of 12-24 months. Moreover, villous atrophy with negative serology of CD can occur in various conditions so it is mandatory to keep in mind that SNCD comes into the differential diagnosis with many other sprue-like enteropathies (13) subdivided into different categories including Autoimmune, Neoplastic, Infiltrative, Infectious, etc. (14-16) autoimmune enteropathy, small intestine bacterial overgrowth, eosinophilic gastroenteritis, common variable immunodeficiencies (CVID), tropical sprue, drug-induced enteropathy, indolent CD4+ T cell lymphoma, giardiasis, and idiopathic villous atrophy are some example disease conditions(16) Before making a definitive diagnosis of SNCD, it is crucial to rule out other possible causes of villous atrophy to avoid needless lifestyle GFDs (17).

According to the pathophysiology of SNCD, two theories have been proposed: deposition of anti-tTG immune complexes in the duodenal mucosa, preventing anti-tTG from entering the bloodstream, or insufficient antibody synthesis by plasma cells (1).

Due to the difficulty and delay in SNCD diagnosis, and the fact that these individuals may have a poor prognosis and a high risk of developing complications, it is critical to understand the prevalence of SNCD and detect them promptly. This study aims to determine the prevalence of SNCD and compare clinical and laboratory findings between seronegative and seropositive celiac disease patients in northeast Iran.

Methods

This was a retrospective analysis of patients referred to the Celiac Disease Center in Mashhad (Iran) between 2010 and 2020. The ethical committee of Mashhad University of Medical Sciences has authorized this work (code: IR.MUMS.MEDICAL.REC.1400.089). It was additionally certifying that all subjects and their legal guardian provided informed consent.

Criteria for cohorts

CD confirmed with symptoms of CD, positivity of serum CD autoantibodies, villus atrophy in duodenal biopsy; and in some patients using human leukocyte antigen (HLA)-DQ2 or DQ8 genotypes, and clinical and pathologic response to the gluten-free diet (GFD) which defines regrowth of villi after 12 months of GFD.

All patients who underwent an endoscopy and were diagnosed with duodenal mucosal atrophy and referred to a celiac clinic as CD patients were included. Both

TTG IgA/and total IgA IgG antibodies were examined for all cases. Patients who tested negative for TGA IgA but had normal serum IgA level were sent for TTG IgG or DGP IgG, stool examination for white blood cell-red blood cell (WBC-RBC), ova, and parasite. Any history of infection, giardia, inflammatory bowel disease, or HIV, as well as medication use before biopsy, were obtained.

Mucosal lesions were classified using a modified Marsh classification. Patients with a negative TGA-IgA level, normal IgA total level, and a Modified Marsh Classification grade > 1 were referred to an expert pathologist in this field to review the biopsy specimen and repeat serology. For individuals with IgA deficiency, further IgG-based serology for celiac disease was performed, and if these antibodies were positive considered as CD with IgA deficiency and if serology IgG were negative, the patient was considered to have SNCD. By confirming pathology and serology, individuals were classified as having SNCD if they had positive DQ2-DQ8 and remission of clinical symptoms. Clinical assessment every 3 months and histologic evaluation after 12 months of GFD were done. All patients had rebiopsy after 12 months of GFD. We rely on challenge testing by Gluten containing diet for next 12 months and re-biopsies (third time of biopsy)in patients who didn't have genetic testing or had only histologic healing without clinical improvement after 12 months of GFD. Positive challenge test which defined by recurrence of histologic marker of CD with regular diet, confirmed SNCD.

Densitometry of Lumbar spine and femoral in patients more than 30 years old was done and bone loss evaluated by Z score in premenopausal female and male less than 55.

Overall, 1123 patients with villous atrophy were enrolled in this study. 8 cases were excluded from statistical analysis since they were three cases of Crohn's disease, two cases of common variable immunodeficiency, two drug users (Losartan and Pb), and one case of peptic duodenitis so these 8 patients with villous atrophy and negative serology were ruled out from CD diagnosis. However, statistical analysis was performed on 1115 patients diagnosed with CD.

Statistical analysis

Data were analyzed using SPSS software (21, SPSS Inc., Chicago). STATA was used for data examination. The prevalence of SNCD was determined in this cohort, and laboratory testing, pathology, and clinical findings were compared between seropositive and seronegative CD. Participants' qualitative features are quantified using frequency and percentage, while their quantitative traits are quantified using mean and standard deviation. Additionally, Mann-Whitney Test, Chi-square, and T-test statistical tests were used for each of the comparisons within the subgroups. The significance level for all tests was 0.05.

There is also the presence of missing data in their laboratory tests (Vit D -BMD -family history) in our study. Half of 1115 patients because of age less than 30 or other limitation didn't have densitometry. Some patients didn't agree to go for screening of first-degree relatives.

Results

This study reviewed 1123 patients referred to the Celiac Disease Center for CD diagnosis over ten years. Further differential diagnoses revealed that three out of 35 seronegative had Crohn's disease, two had common variable immunodeficiency (CVID), two had drug-induced enteropathy, and one had peptic duodenitis. These eight were ruled out from our analysis.

Of the 1115 final subjects included in our analysis 27 (2.4%) had SNCD and 1088 (97.5%) had SPCD also four cases of IgA deficiency were detected.

In all, 788 (70.7%) female cases with 19 (2.4%) SNCD between them showed females predominance in both groups with a gender ratio (f/m) of 2.0 in SNCD patients.

The total mean age was 29.7±15.7 years (1 to 76 years), while the mean age of patients with SNCD was 37.1±16.3 years (6 to 63 years). The mean BMI of SNCD and SPCD patients was 23.9 and 21.4, respectively (P=0.02). Only two (13%) of the 15 SNCD patients with a documented family history had at least one SPCD relative. Patients with SPCD had a more favorable family history than those with SNCD, although the difference is not statistically significant (P=0.38) (Table 1).

All SNCD patients (100%) (Marsh 2&3) and 95.6 percent of SPCD patients had Villous atrophy (P=0.88). 60% of SNCD patients and 84.5% of SPCD patients had scalloping and fissuring in their duodenal biopsies (P=0.17) (Table 1). The gastrointestinal manifestations

Table 1. Demographic data.

Variable	Total (n=1115)	SNCD (n=27)	SPCD (n=1088)	P-value
Age; mean ± SD, years (min, max)	29.7± 15.7, (1 - 76)	37.1 ± 16.3, (6 -63)	29.5 ± 15.7, (1-76)	0.01*[a]
BMI; mean ± SD, (min, max)	21.4±5.2, (9.2 -42.8)	23.9±5.3, (12.8-33.3)	21.4±5.2, (9.21-42.8)	0.02*[a]
SGOT(U/L); mean rank, (min, max)	(1.20-112)	317.4 (1.2-112)	354.9, (0- 585)	0.41[b]
SGPT(U/L); mean rank, (min, max)	(4.30-452)	281.8 (11-156)	354.6, (0- 452)	0.10[b]
Sex; n (%)				0.96[c]
female	785 (70.7)	19 (70.4)	766 (70.7)	
male	325 (29.3)	8(29.6)	317 (29.3)	
Familial history of CD; n (%)				0.38[d]
Yes	179 (24.1)	2 (13.3)	177 (24.3)	
No	453 (60.9)	9 (60.0)	444 (60.9)	
Undetermined	112 (15.1)	4 (26.7)	108 (14.8)	
Marsh; n (%)				0.88[d]
I	42 (4.1)	0	42 (4.2)	
II	55 (5.4)	1 (3.8)	54 (5.4)	
III	927 (90.3)	25 (96.2)	902 (90.1)	
Pathology; n (%)				0.17[d]
Scalloping & fissuring	363 (84.2)	3 (60.0)	360 (84.5)	
Others	68 (15.8)	2 (40.0)	66 (15.5)	
Main symptoms; n (%)				
Gastrointestinal	702 (65.3)	19 (73.1)	683 (65.1)	0.65[c]
Diarrhea	425 (41.9)	11 (44.0)	414 (41.9)	0.85[c]
Flatulence	574 (60.5)	19 (76.0)	555 (60.1)	0.08[c]
Dyspepsia	248 (23.2)	2 (28.6)	146 (42.8)	0.70[d]
Main complication; n (%)				
Anemia	475 (53.1)	10 (50.0)	465 (53.1)	0.70[c]
LFT abnormality	295 (32.3)	3 (13.0)	292 (32.8)	0.10[d]
Dermatitis herpetiform	32 (13.0)	0	32 (13.1)	0.99[d]
Neurologic disorders	436 (57.7)	10 (55.6)	426 (57.7)	0.84[c]
Vitamin D levels (ng/ml); n (%)				0.37[d]
Normal	243 (35.7)	4 (21.1)	239 (36.2)	
Low	214 (31.5)	8 (42.1)	206 (31.2)	
Insufficient	223 (32.8)	7 (36.8)	217 (32.7)	
Metabolic bone disorder (Femur); n (%)				0.83[d]
Normal	251(48.6)	7 (43.8)	244 (48.8)	
Osteoporosis	75 (14.5)	3 (18.8)	72 (14.4)	
Osteopenia	190 (36.8)	6 (37.5)	184 (36.8)	
Metabolic bone disorder (Spine); n (%)				0.22[d]
Normal	257 (50.0)	8 (50.0)	249 (50.0	
Osteoporosis	84 (16.3)	5 (31.3)	79 (15.9)	
Osteopenia	173 (33.7)	3 (1.8)	170 (34.1)	
TPO levels (IU/ml); n (%)				0.80[d]
Normal	244 (63.0)	7 (58.3)	237 (63.2)	
High	137 (35.4)	5 (41.7)	132 (35.2)	
Low	6 (1.6)	0	6 (1.6)	
Autoimmune Diseases; n (%)				0.50[d]
no	944 (85.0)	23 (85.2)	921 (85.0)	
Thyroid diseases	102 (9.2)	3 (11.1)	99 (9.1)	
Diabetes Mellitus	65 (17.7)	1 (3.7)	64 (5.9)	

[a] t-Test. [b] Mann-Whitney U. [c] Pearson Chi-Square test. [d] Fisher's Exact Test.

of SPCD were shown in the majority of SNCD patients (73.1%) and 65.1 percent of SPCD patients (P=0.65). Chronic diarrhea occurred in 44 percent of SNCD patients, and dyspepsia occurred in 28.6 percent (P>0.05); moreover, flatulence occurred in 76 percent of SNCD and 60.1 percent of SPCD patients (P=0.08). Both groups exhibit nearly identical clinical manifestations, and there was no statistically significant difference between intestinal and extra-intestinal signs. In SNCD patients, the most common manifestations were 50% anemia, 55.6 percent neurological symptoms, and 13% liver function tests (LFT) abnormality (P>0.05). Dermatitis herpetiformis was

reported in 13% of SPCD patients, while none of the SNCD patients had dermatitis herpetiformis.

Vitamin D levels were normal in four (21.1%) SNCD patients. Thyroid peroxidase (TPO) levels were within the normal range in 58.3 percent of SNCD, whereas 41.7 percent had high TPO. LFT was reported as SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase) levels in both groups (P=0.33, P=0.11 respectively). Overall, cases with the report of SGPT or SGOT around 300 U/L (units per liter of serum) were because of comorbidity of autoimmune hepatitis and celiac. SNCDs had a higher rate of co-occurrence with thyroid diseases than SPCDs (11.1 percent in SNCDs versus 9.1 percent in SPCDs, (P=0.50), and SPCDs had a higher rate of co-occurrence with diabetes mellitus than SNCDs (5.9 percent in SPCDs versus 3.7 percent in SNCDs). However, these differences were not statistically significant (P=0.5) (Table 1).

Bone densitometry of Lumbar spine and femoral was done for premenopausal female and men less than 55 and more than 30 years old. The femoral densitometry analysis in SNCD group revealed 3 cases of osteoporosis and 6 cases of osteopenia, and in SPCD group revealed 72 cases of osteoporosis and 184 cases of osteopenia. In contrast, the Lumbar spine densitometry analysis in SNCD group revealed 5 cases of osteoporosis and 3 cases of osteopenia and in SPCD group.

Discussion

SNCD was 2.4 percent prevalent in 1123 patients with mucosal atrophy and in 1115 patients with CD in our study. The mean age of patients with SNCD resulted to be significantly higher than that of SPCD patients (p=0.01). Patients' gender was unrelated to their SNCD status. In this study, SNCD was the most frequent cause of seronegative villous atrophy, consistently with the results obtained by Volta et al (18) SNCD exhibited total or partial villous atrophy with only one patient showing increased intraepithelial lymphocytes (IELs) and crypt hyperplasia (Marsh2), accordingly with other studies (19).

Because SNCD patients were diagnosed based on duodenal biopsy pathology, their histological study revealed characteristics consistent with celiac disease, and the most prevalent stage was Marsh 3. (96.4 percent). Additionally, scalloping and fissuring were detected in 66.7 percent of duodenal biopsies of patients with SNCD. Furthermore, nearly 90% of all SNCD and SPCD patients had villous atrophy (Marsh 3). The prevalence of SNCD was 2.4 percent in our study, Abram et al. reported that 15% of patients with villous atrophy had negative serology (20), and Rostami et al. said a 70% co-occurrence of partial villous atrophy with negative serology in a comparable study. Additionally, their study found that both SNCD and SPCD patients had similar clinical presentations and improved following GFD (21).

The liver and celiac disease (CD) share a complex relationship. While in some patients, isolated hypertransaminasemia is the only manifestation of CD, liver diseases may also be associated with the presence of isolated tissue transglutaminase antibodies IgA (tTG IgA) without histologic evidence of CD (22).

SNCD patients presented clinically similarly to SPCD patients (23); dyspepsia was the most often reported symptom, followed by diarrhea, anemia, and neurological signs. Flatulence was the most frequently linked symptom in dyspeptic patients (74 percent). According to prior research, dermatitis herpetiformis is strongly associated with SPCD; however, none of the SNCD patients in our study had this symptom. Although there was no statistically significant difference between the two groups in terms of autoimmunity, thyroid disorders, and diabetes coexistence, although diabetes type 1 is more frequent in SPCD than in SNCD which can be due to low sample size of SNCD.

Delay diagnosis in SNCD probably due to negative screening test of serology for CD. The average age of SNCD patients was significantly higher than that of SPCD ones. Similarly, to our research, Volta et al found that 1.7 percent of patients had SNCD, and the median age of these patients was significantly higher than SPCDs at the time of diagnosis, which is likely due to a later diagnosis than SPCDs. As a result, they discovered a clear relationship between SNCD and more severe degrees of villous atrophy; in contrast, two other investigations (19) and (24) found that SPCDs were linked with a greater degree of villous atrophy than SNCDs. Additionally, they discovered that SNCDs had more traditional clinical signs than the

SPCD group (18), although clinical manifestations were comparable in our study's two groups.

After CD (97 percent), the most prevalent cause of villous atrophy in the duodenum is SNCD (2.4 percent). Between seronegative villous atrophies, most common cause in our area were SNCD (77%) followed by inflammatory bowel disease (IBD) (8.5 percent), common variable immunodeficiency (CVID) (5.7 percent), medication use, and duodenitis (5.7 percent) (2 percent). In our CD group, the prevalence of IgA deficiency was 0.3 percent.

This study sets out to examine the prevalence, clinical characteristics, and pathologic aspects of SNCD and SPCD. This is the first study to our knowledge in the northeast of Iran on the prevalence, pathophysiology, and clinical characteristics of SNCD.

Conclusion

2.4% of CD patients have negative serology (SNCD) which make a delay in their diagnosis and can predispose them to more complication. Age and BMI of SNCD are higher than CD at the time of diagnosis. Careful attention is necessary to diagnosis SNCD and determine other possible cause of seronegative villous atrophy or enteropathies. Accurately in our study, the most common cause of seronegative enteropathy is SNCD (77%) fallowed by IBD (8.5%) and CVID (5.7%) drug (5.7%) and peptic duodenitis (2%).

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Conflict of interests

There are no financial conflicts of interest to disclose for any authors.

References

1. Ríos León R, Crespo Pérez L, Rodríguez de Santiago E, Roy Ariño G, De Andrés Martín A, García Hoz Jiménez C, et al. Genetic and flow cytometry analysis of seronegative celiac disease: a cohort study. Scand J Gastroenterol 2019;54:563-570.

2. Tye-Din JA, Galipeau HJ, Agardh D. Celiac disease: a review of current concepts in pathogenesis, prevention, and novel therapies. Front Pediatr 2018;6:350.

3. Choung RS, Larson SA, Khaleghi S, Rubio-Tapia A, Ovsyannikova IG, King KS, et al. Prevalence and morbidity of undiagnosed celiac disease from a community-based study. Gastroenterology 2017;152:830-839.

4. Sahin Y. Celiac disease in children: a review of the literature. World J Clin Pediatr 2021;10:53.

5. Ganji A, Esmaielzadeh A, Aafzal Aghayee M, Goshayeshi L, Ghaffarzadegan K. The clinical presentation of celiac disease: experiences from northeastern iran. Middle East J Dig Dis 2014;6:93-97.

6. Jamma S, Rubio-Tapia A, Kelly CP, Murray J, Najarian R, Sheth S, et al. Celiac crisis is a rare but serious complication of celiac disease in adults. Clin Gastroenterol Hepatol 2010;8:587-590.

7. Salmi T, Hervonen K, Reunala T. Dermatitis herpetiformis--a cutaneous manifestation of coeliac disease. Coeliac Disease and Gluten-Related Disorders. 2022:161-177.

8. Kárpáti S. An exception within the group of autoimmune blistering diseases: dermatitis herpetiformis, the gluten-sensitive dermopathy. Dermatol Clin 2011;29:463-468.

9. Van Kalleveen MW, de Meij T, Plötz FB. Clinical spectrum of paediatric coeliac disease: a 10-year single-centre experience. Eur J Pediatr 2018;177:593-602.

10. Ganji R, Moghbeli M, Sadeghi R, Bayat G, Ganji A. Prevalence of osteoporosis and osteopenia in men and premenopausal women with celiac disease: a systematic review. Nutr J 2019;18:9.

11. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 2013;108:656-676.

12. Goebel SU. What is the prevalence of Seronegative celiac disease (sprue)? [cited at 26/9/2020] Available from: https://emedicine.medscape.com/article/171805-questions-and-answers.

13. Jansson-Knodell CL, Hujoel IA, Rubio-Tapia A, Murray JA. Not all that flattens villi is celiac disease: a review of enteropathies. Mayo Clin Proc 2018;93:509-517.

14. Malamut G, Verkarre V, Suarez F, Viallard JF, Lascaux AS, Cosnes J, et al. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. Am J Gastroenterol. 2010;105:2262-2275.

15. Wittich CM, Ed. Mayo Clinic Internal Medicine Board Review. 12th ed. USA: Oxford University Press; 2019.

16. Kumar V, Abbas A, Aster JC, Eds. Robbins & Cotran Pathologic Basis of Disease. 10th ed. Amsterdam, Netherlands: Elsevier; 2010. p.1450-1450.

17. Schiepatti A, Sanders DS, Baiardi P, Caio G, Ciacci C, Kaukinen K, et al. Nomenclature and diagnosis of seronegative coeliac disease and chronic non-coeliac enteropathies in adults: the Paris consensus. Gut 2022;71:2218-2225.

18. Volta U, Caio G, Boschetti E, Giancola F, Rhoden KJ, Ruggeri E, et al. Seronegative celiac disease: Shedding light on an obscure clinical entity. Dig Liver Dis 2016;48:1018-1022.

19. Farina MH, Kumar Mandhwani R, Hassan Luck N, Abbas Z, Mubarak M, Laeeq SM, et al. Clinicopathological study of seronegative celiac disease in adults in Pakistan: a pilot study. Middle East J Dig Dis 2017;9:94-99.

20. Abrams JA, Diamond B, Rotterdam H, Green PH. Seronegative celiac disease: increased prevalence with lesser degrees of villous atrophy. Dig Dis Sci 2004;49:546-550.

21. Rostami K, Kerckhaert J, Tiemessen R, von Blomberg BM, Meijer JW, Mulder CJ. Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice. Am J Gastroenterol 1999;94:888-894.

22. Cvetkovic L, Bernard G, Galette N, Hétu PO, Vincent C, Bouin M, et al. Discordance between serology and histology for celiac disease in a cohort with coexisting liver disorders. J Can Assoc Gastroenterol 2020;3:185–193.

23. Dore MP, Pes GM, Dettori I, Villanacci V, Manca A, Realdi G. Clinical and genetic profile of patients with seronegative coeliac disease: the natural history and response to gluten-free diet. BMJ Open Gastroenterol 2017;4:000159.

24. Ramakrishna BS, Makharia GK, Chetri K, Dutta S, Mathur P, Ahuja V, et al. Prevalence of adult celiac disease in India: regional variations and associations. Am J Gastroenterol 2016;111:115-123.