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Gluten Exposure Can Trigger a Silent Autoimmune Disorder in Celiac Disease: Five Case Reports

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Abstract People with celiac disease are at increased risk of developing other autoimmune disorders. Leaving the gluten-free diet not only causes the recurrence of celiac disease, but also increases the incidence of other autoimmune disorders. Here, we present 5 cases suffering from other autoimmune diseases in addition to background celiac disease. Careful and continuous monitoring of these patients can greatly prevent the occurrence of other autoimmune disorders.

Keywords: *celiac, gluten free diet, autoimmune disorder*

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1. Introduction

Celiac ailment is an immune-mediated situation characterized by small intestinal enteropathy, systemic signs and symptoms associated with malabsorption, immune activation leading to Auto-antibody formation against tissue transglutaminase (tTG) and endomysial autoantigens [1]. Typical presentations of celiac disease include: diarrhea, constipation, weight loss, abdominal pain, and bloating. Also, there are some atypical symptoms including growth failure, iron deficiency anemia, neurologic symptoms, abnormal liver biochemistry, infertility, metabolic bone disease, delayed puberty and Fatigue [1]. In a systematic review, the prevalence of celiac disease has been reported 1.4% based on serologic test results and 0.7% based on biopsy results [2]. It is well known that celiac disease is accompanied by some other autoimmune diseases up to 25% [3]. Symptoms of celiac can be interpreted as originating from different autoimmune diseases [4]. This fact is attributed to both patient's environment and genetic background. There are little studies working on pathways that celiac disease and other autoimmune disorders can influence each other. Gliadin as an important component of gluten has presented cross reaction with autoantigens like pancreatic B cells, synovial cells and thyroid cells leading to insulin-dependent diabetes [5], rheumatoid arthritis [6], and autoimmune thyroid diseases [7]. Gut microbiota dysbiosis, changes in intestinal permeability, and essential micronutrient deficiencies are also introduced as triggering factors for autoimmune disorders. Gliadin maldigestion is also of great importance as an inciting immune response against intestinal wall leading to inflammation and IBS-like symptoms [8]. Additionally, it is proposed that exposure of an immature immune system to gliadin in patients with gluten sensitivity can trigger other immune-mediated disorders [9]. Presence of a large number of autoantibodies against different systems and organs in patients with celiac disease is also another indicator of celiac disease accompaniment to other autoimmune disorders. With this regard, long duration of exposure to gluten antigen is postulated to be a triggering factor for other autoimmune diseases in patients with celiac disease [10]. In present study we have presented 5 known cases of celiac disease who have stopped their gluten-free diet and referred to our medical center with refractory celiac disease and symptoms associated with other autoimmune diseases that were not manifest earlier.

Case report 1

The patient is a 54-year-old woman who presented to the emergency department with complaint of a non-positional abdominal pain aggravating by eating. She had recently developed watery diarrhea and mild jaundice. Investigating her past medical history showed a documented celiac disease (she had not received a gluten-free diet during the last months), Hypothyroidism from 15 years ago, diabetes from 15 years ago and Psoriasis from 10 years ago. Drug history was included levothyroxine, pantoprazole, aspirin, atorvastatin, aetformin, and gloripa. Physical examination was remarkable for icteric skin and sclera, scaly psoriatic lesions on extensors, and tenderness on deep palpation. Report of primary lab tests revealed FBS: 191 mg/dl (100-125), HbA1C: 8.2% (<5.7%), anti

endomysial IgA: 41.9 units (<0.1U), anti-gliadin IgA:14.8 units/l (0-175 U/L), TSH: 5.7 miU/l (0.5-5 miU/l), HLA-DQ2: positive, HLA_DQ8: negative, Bili T: 6.1 mg/dl (<1mg/dl), Bili D: 1.9 mg/dl (0-0.3 mg/dl), AST: 901 IU/l (8-33 IU/l), ALT: 1870 I IU/l (4-36 IU/dl), Alkp: 452 IU/L (44-315 IU/l). Pattern of liver enzymes aroused suspicion of a hepatocellular injury. Secondary workups were followed for hepatic injury including viral markers, serum iron level, and evaluation of 24-hour urine copper which were all within normal ranges except for autoantibodies which were higher than the upper limit of normal for ANA and ASMA. Abdominopelvic imaging was normal. Biopsies taken from second part of duodenum in gastroscopy were consistent with MARSH2 indicating damage of villi in a patient who has not followed a strict gluten-free diet. The patient was started on prednisolone and Azathioprine regimen for autoimmune hepatitis and was advised to go on a strict gluten-free diet. She showed gradual improvement and finally achieved a complete biochemical response. It is driven from the case that cessation of the gluten-free diet had led to an increase in liver enzymes and the occurrence of autoimmune hepatitis.

Case report 2

A 44-year-old woman known case of celiac disease and hypothyroidism on gluten-free diet and levothyroxine since 2011. Her family history was positive for diabetes and myocardial infarction (MI) at the age of 37 in mother, diabetes in father and hypothyroidism in sister. She presented with sagittal sinus thrombosis plus arthralgia after a long course of non-adherence to gluten-free diet. With the diagnosis of antiphospholipid syndrome (APS), she was treated with intravenous methylprednisolone and cyclophosphamide pulses. After discharge, she continued prednisolone, warfarin and rivaroxaban. Despite these treatments, she had recurrent deep vein thrombosis (DVTs). Due to frequent DVTs, the patient underwent IVC venography and iliac venoplasty with three stents implementation. She referred to the medical center for further follow-ups which revealed weight loss (6 kg), diffuse abdominal pain, frequent bowel movements (10-12 time in a day), and non-bloody diarrhea since one month before admission. Investigating the laboratory tests showed anti-TPO: 95.42 IU/ml (<34 IU/l), anti tTG IgA: >200 U/ml (4-10 U/ml), morning cortisol level: 7.07 mcg/dl (10-20 mcg/dl), Hb: 11.3 g/dl (12-15 g/dl for women), and MCV: 83 fl (80-100 fl). Based on bone mineral densitometry, T-score was -1.6 in lumbar spines indicative of osteopenia. Abdominopelvic ultrasound was normal. Color doppler ultrasound revealed venous stents in the common external iliac vein and proximal & distal parts of femoral veins where normal venous flow with respiratory changes was seen and no evidence of thrombosis was detected. Biopsies from bulb and second part of duodenum were indicative of active phase of celiac disease with complete atrophy and intraepithelial lymphocytes (IELs) more than 30/100 (MARSH 3C). The patient was continued with prednisolone, rivaroxaban and hydroxychloroquine and was put on gluten-free diet. She improved gradually and now is under regular follow-ups. Little is known about the accompaniment of celiac disease and APS. More studies are required in this field to endorse this association But, presentation of thromboembolic events simultaneous with gluten-rich diet and reappearance of celiac disease symptoms arouses suspicion of association between celiac disease and APS.

Case report 3

A 29-year-old woman with symptoms of abdominal pain, chronic diarrhea, weight loss of 20kg, fatigue during the previous 6 months, and amenorrhea from 3 months ago referred to the medical center. Her past medical history showed vitiligo and hyperthyroid disorder. She used topical betamethasone and methimazole. On general physical examination, the patient had 2+ pitting edema on both lower limbs, disseminated white lesions on limbs and knees, tenderness in left lower quadrant (LLQ), arthralgia, no ascites, no skin rash, and no dermatitis herpetiform. All new symptoms were started after stopping the gluten-free diet. Investigations of laboratory data revealed a mild increase in liver enzymes AST: 196 IU/l (8-33 IU/l), ALT: 113 IU/l (4-36 IU/dl), ALKP: 175 IU/l (44-315 IU/l). Other laboratory tests include Hb: 12.3 gr/dl (12-15 g/dl), MCV: 67 fl (80-100 fl), Alb: 3.1 gr/dl (3.4-5.4 gr/dl), Ca: 7.9 mg/dl (8.6-10.3 mg/dl), Ferritin: 18.8 mcg/l, TSH<0.004 (0.5-5 miU/l), anti tTG: 543.73 U/ml (4-10 U/ml), anti endomysial IgA: positive (negative <0.1U), stool calprotectin: 710 µg/mg (10-60 µg/mg), stool W.B.C: 2-3/hpf (<5/hpf) and R.B.C: 1-2/hpf (<3/hpf). Abdominopelvic ultrasound was unremarkable except for dilatation of the small intestine loops and increased wall thickness of the small bowel loops indicating the probability of inflammatory bowel disease which was confirmed in CT and MR evaluations. Endoscopy was performed which revealed scalloping folds and nodularity in D2 with biopsies compatible with MARSH 3 of celiac disease. Colonoscopic examination of the mucosa of the rectum, sigmoid, and descending colon was consistent with Mayo-endoscopic score of 2. Biopsies from the involved mucosa confirmed the diagnosis of inflammatory bowel disease. The patient was continued with prednisolone and azathioprine. She was also suggested to have a gluten-free diet. She was found to be dependent to steroids as she was not able to lower prednisolone to less than 10 mg per day. A comprehensive interview with the patient established non-adherence to gluten-free diet. Before initiating a step-up approach followed by an anti TNF, she was put on a strict gluten-free diet which let the patient gradually taper the prednisolone without any disease flare up. Finally, she continued azathioprine and gluten-free diet. The presented case is a simultaneous presentation of celiac disease and inflammatory bowel disease who improved by simultaneous treatment of gluten-free diet and immunosuppressants which is indicative of the importance of gluten-free diet in such patients. Although steroids are accepted as effective induction therapy for celiac disease, but hey are suggested to add as an adjunct to the gluten-free diet to improve the efficacy of regimen and are not suggested to be used without restriction of gluten.

Case report 4

The patient is a 37-year-old woman with celiac disease (from 10 years ago) who had stopped gluten-free diet

since 1 year ago referred by massive hematemesis, epigastric pain and hypermenorrhea. Her past medical history was positive for osteopenia in bone mineral densitometry, hypothyroidism, and history of 2 miscarriages in the first trimester. Past drug history was positive for atorvastatin, folic acid, ferrous sulphate, and levothyroxine. On admission, she had hypotension, pale conjunctiva, and ecchymosis throughout the body. After complete resuscitation, an emergent endoscopy was performed which revealed a small-sized hiatal hernia and oozing from the mucosa of antrum and body. Gynecologic examinations and ultrasound studies were unremarkable. Due to simultaneous presentation of GI bleeding, ecchymoses and hypermenorrhea, coagulopathies were suspected and hematology consultation was requested. Results showed factor II= 20% and factor V= 74%, factor VII<1%, factor VIII:C= 81%, factor IX= 5%, factor X= 8%, factor XI= 50% (50-150% of activity in pooled normal plasma), PTT-LA screen= 66.5 sec (25-35 sec), PTT-LA mix= 47 sec (25-35 sec), Dilute Russell Viper Venom Time (DRVVT) screen= 126 sec (29-42 sec), DRVVT confirm= 80.5 sec, DRVV ratio= 1.57 (<1/20), prolonged PT, and normal complete blood counts suspicious to vitamin K deficiency. Elective endoscopy revealed nodularity in bulb and scalloping folds in D2. Diagnosis was severe chronic atrophic duodenitis consistent with celiac disease, MARSH 3c. The patient was continued with prednisolone, vitamin K and gluten free diet. She improved gradually and now is under regular follow up. It is necessary to mention that association between vit K deficiency and celiac disease is not completely understood. But it is suggested that inflammatory changes in the small intestine as could be seen in celiac disease would affect absorption of vit k.

Case report 5

A 42-year-old man known case of celiac disease since childhood presented with complaint of right upper quadrant (RUQ) abdominal pain, jaundice, melena, and hematemesis. He reported a weight loss of 18 kg over the past two years. He had a proper follow up and gluten-free diet until 5 years ago. His family history was positive for hypothyroidism in parents and siblings. On arrival to the emergency department, physical examination was indicative of vitiligo lesions initiating from 2 years ago, icterus, tenderness in RUQ in deep touch, and splenomegaly. Evidence of ascites and encephalopathy was not detected in examination. An upper endoscopy was performed which showed one row of small straight varices in lower third of esophagus. Colonoscopy was done which was highly suggestive for inflammatory bowel diseases (IBD). Pathologic examination also confirmed the diagnosis. Abdominopelvic CT-scan MRI/MRCP detected cirrhotic changes in the liver, splenomegaly (craniocaudal span= 203mm), and many portosystemic collaterals. Dilatation of intrahepatic bile ducts with beaded and irregular appearance was evident. The main branches of the portal vein and hepatic artery were intact. The findings were suggestive of IBD followed by liver cirrhosis in the context of primary sclerosing cholangitis (PSC). Close follow-ups until 5 years ago suggest that the recent presence of vitiligo and symptoms related to the UC and PSC might be attributed to gluten-rich diet in the last 5 years.

2. Discussion

Autoimmune diseases are situations initiated with the lack of immunological tolerance to self-antigens and that makeup, a heterogeneous institution of problems wherein a couple of changes within side the immune machine bring about a collection of syndromes that both goals unique organs or have an effect on the body systematically [11].

The present study confirms the accompaniment of autoimmune diseases with celiac disease and also suggests the probability of appearance of some of these disorders in presence of gluten-rich diet. Celiac disease is an important autoimmune disease that have coexistence with the other autoimmune diseases [12]. In the case of the described patients with celiac we looked into other autoimmune disorders as the result of leaving gluten-free diet include vitamin K deficiency, vitiligo, autoimmune hepatitis, thyroid dysfunction and psoriasis. Since the celiac is triggered by gluten [13], we assumed leaving the gluten-free diet lead to the other autoimmune disorders and even a rise in the liver enzymes. In patients who consume gluten for a long time, the intestinal barrier associated with celiac disease is disturbed and the permeability to immune stimulants increases, as a result, the incidence of autoimmune diseases increases [14].

The detection of anti-tissue transglutaminase immunoglobulin A (anti-tTG IgA), anti-endomysial antibody (EMA), and anti-gliadin antibody performs a vital position withinside the prognosis of celiac disease[15]. In presented cases we could see rise of these antibodies simultaneous with recurrence of symptoms of celiac disease as the result of leaving the gluten-free diet.

The presented cases had thyroid dysfunction. There are a strong association between thyroid dysfunction and celiac disease [16]. Some studies have indicated the existence of a common genetic background with T-cell mediation [17,18]. In the present cases, they reported a medical family history of thyroid disease. it seems that the coexistence of autoimmune thyroid disease and celiac disease is thought to be due to a common genetic predisposition [12]. Other studies confirm the coexistence of celiac with thyroid dysfunctions [4,19]. Freeman in 2016 base on the review of various studies demonstrated that this coexistence could be genetically related to determination of owing to the common detection of human lymphocyte antigen (HLA) haplotypes in most with autoimmune thyroid disease and celiac [20].

The patients had feature of dermatological disease like vitiligo and psoriasis. Previous studies confirmed the relationship between celiac and immune-related skin diseases [21] [22]. In a meta-analysis study, the prevalence of vitiligo in patients with celiac disease was reported from 0.2 to 9% [22]. Elimination of gluten can help improve the symptoms of patients with psoriasis, and vitiligo, who are seropositive for CD-related autoantibodies [23]. Celiac disease has highly association with interleukin (IL)-2, IL-6, IL-17, and IL-21 [24] [25] which also play important roles in the pathogenesis of vitiligo [26]. Regarding the relationship between celiac disease and psoriasis, it has been mentioned that in celiac patients who are exposed to gliadin, CD4 + T cell responses are stimulated and as a result, they produce high levels of

gamma interferon [27] [28].

Symptoms of autoimmune hepatitis in the first case as well as symptoms of other autoimmune disorders in the next cases which presented after reintroduction of gluten to their diet suggest the probability of relation between gluten consumption and appearance of autoimmune disorders in patients with documented celiac disease. A meta-analysis study in 2021 estimated the prevalence of celiac disease in patients with autoimmune hepatitis to be about 3.5% [29]. Consumption of gluten-containing food can lead to increased intestinal permeability with circulating and residual tissue transglutaminase antibodies in the liver, which modify self-antigens to cause liver damage [30]. Given that celiac disease is associated with liver disease, avoiding a gluten-containing diet has been proven to improve liver damage in celiac-related hepatitis [31] [32]. Same genetic loci for Human Leukocyte Antigen class II, in celiac and autoimmune hepatitis bring about their coexistence [29]. So, it is recommended that an elevation in aminotransferases persisting after a gluten-free diet and worsening after cessation of gluten-free diet should be taken into account for an alarming sign of coexisting autoimmune liver disease. Presence of autoantibodies should be carefully worked up in order to avoid misdiagnosis of autoimmune hepatitis which can result in a delay in treatment and progression of disease.

3. Summery

People with celiac disease are at increased risk of developing other autoimmune disorders. Leaving the gluten-free diet not only causes the recurrence of celiac disease, but also increases the incidence of other autoimmune disorders. It seems that genetic factors and pathogenic relationships both be involved in this pathogenesis. Careful and continuous monitoring of these patients can greatly prevent the occurrence of other autoimmune disorders.

References

[1] Lebwohl B, Rubio-Tapia A. Epidemiology, presentation, and diagnosis of celiac disease. Gastroenterology. 2021; 160(1): 63-75.

[2] Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global prevalence of celiac disease: systematic review and meta-analysis. Clinical gastroenterology and hepatology. 2018; 16(6): 823-36. e2.

[3] Madan Mohan P, Ramesh T. Multiple autoimmune syndrome. Indian Journal of Dermatology Venereology and Leprology. 2003; 69: 298-9.

[4] Zwolińska-Wcisło M, Galicka-Latała D, Rudnicka-Sosin L, Rozpondek P. Coeliac disease and other autoimmunological disorders coexistance. Przeglad Lekarski. 2009; 66(7): 370-2.

[5] Prieto J, Singh KB, Nnadozie MC, Abdal M, Shrestha N, Abe RAM, et al. New Evidence in the Pathogenesis of Celiac Disease and Type 1 Diabetes Mellitus: A Systematic Review. Cureus. 2021; 13(7).

[6] Bruzzese V, Scolieri P, Pepe J. Efficacy of gluten-free diet in patients with rheumatoid arthritis. Reumatismo. 2020; 72(4): 213-7.

[7] Knezevic J, Starchl C, Tmava Berisha A, Amrein K. Thyroid-gut-axis: how does the microbiota influence thyroid function? Nutrients. 2020; 12(6): 1769.

[8] Naseri K, Dabiri H, Rostami-Nejad M, Yadegar A, Houri H, Olfatifar M, et al. Influence of low FODMAP-gluten free diet on gut microbiota alterations and symptom severity in Iranian patients with irritable bowel syndrome. BMC gastroenterology. 2021; 21(1): 1-14.

[9] Ventura A, Magazu G, Gerarduzzi T, Greco L. Coeliac disease and the risk of autoimmune disorders. Gut. 2002; 51(6): 897-8.

[10] Guidetti CS, Solerio E, Scaglione N, Aimo G, Mengozzi G. Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders. Gut. 2001; 49(4): 502-5.

[11] Marrack P, Kappler J, Kotzin BL. Autoimmune disease: why and where it occurs. Nature medicine. 2001; 7(8): 899-905.

[12] Harpreet S, Deepak J, Kiran B. Multiple autoimmune syndrome with celiac disease. Reumatologia/Rheumatology. 2016; 54(6): 326-9.

[13] Valvano M, Longo S, Stefanelli G, Frieri G, Viscido A, Latella G. Celiac disease, gluten-free diet, and metabolic and liver disorders. Nutrients. 2020; 12(4): 940.

[14] Ventura A, Magazzù G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. Gastroenterology. 1999; 117(2): 297-303.

[15] Leffler DA, Schuppan D. Update on serologic testing in celiac disease. Official journal of the American College of Gastroenterology| ACG. 2010; 105(12): 2520-4.

[16] Baharvand P, Hormozi M, Aaliehpour A. Comparison of thyroid disease prevalence in patients with celiac disease and controls. Gastroenterology and Hepatology from Bed to Bench. 2020; 13(1): 44.

[17] Kurien M, Mollazadegan K, Sanders DS, Ludvigsson JF. Celiac disease increases risk of thyroid disease in patients with type 1 diabetes: a nationwide cohort study. Diabetes Care. 2016; 39(3): 371-5.

[18] Jabri B, Sollid LM. Tissue-mediated control of immunopathology in coeliac disease. Nature Reviews Immunology. 2009; 9(12): 858-70.

[19] Sategna-Guidetti C, Volta U, Ciacci C, Usai P, Carlino A, De Franceschi L, et al. Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian multicenter study. The American journal of gastroenterology. 2001; 96(3): 751-7.

[20] Freeman HJ. Endocrine manifestations in celiac disease. World journal of gastroenterology. 2016; 22(38): 8472.

[21] Lebwohl B, Söderling J, Roelstraete B, Lebwohl MG, Green PH, Ludvigsson JF. Risk of skin disorders in patients with celiac disease: A population-based cohort study. Journal of the American Academy of Dermatology. 2021; 85(6): 1456-64.

[22] Zhang J-Z, Abudoureyimu D, Wang M, Yu S-R, Kang X-J. Association between celiac disease and vitiligo: A review of the literature. World Journal of Clinical Cases. 2021; 9(34): 10430.

[23] Volta U, Bardazzi F, Zauli D, De Franceschi L, Tosti A, Mounaro N, et al. Serological screening for coeliac disease in vitiligo and alopecia areata. British Journal of Dermatology. 1997; 136(5): 801a-2.

[24] Akbulut U, ÇEBİ A, Sag E, İkbal M, Cakir M. Interleukin-6 and interleukin-17 gene polymorphism association with celiac disease in children. Turkish Journal of Gastroenterology. 2017; 28(6).

[25] Ecevit ÇÖ. Interleukin-6 and Interleukin-17 gene polymorphisms and celiac disease susceptibility. Turk J Gastroenterol. 2017; 28: 432-3.

[26] Sushama S, Dixit N, Gautam RK, Arora P, Khurana A, Anubhuti A. Cytokine profile (IL‐2, IL‐6, IL‐17, IL‐22, and TNF‐α) in vitiligo—New insight into pathogenesis of disease. Journal of Cosmetic Dermatology. 2019; 18(1): 337-41.

[27] Abdallah MA, Abdel-Hamid MF, Kotb AM, Mabrouk EA. Serum interferon-g is a psoriasis severity and prognostic marker. Cutis. 2009; 84(3): 163-8.

[28] Nilsen EM, Jahnsen FL, Lundin KE, Johansen FE, Fausa O, Sollid LM, et al. Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease. Gastroenterology. 1998; 115(3): 551-63.

[29] Haggård L, Glimberg I, Lebwohl B, Sharma R, Verna EC, Green PH, et al. High prevalence of celiac disease in autoimmune hepatitis: Systematic review and meta‐analysis. Liver International. 2021; 41(11): 2693-702.

[30] Panetta F, Nobili V, Sartorelli MR, Papa RE, Ferretti F, Alterio A, et al. Celiac Disease in Pediatric Patients with Autoimmune Hepatitis. Pediatric Drugs. 2012; 14(1): 35-41.

[31] Zali MR, Nejad MR, Rostami K, Alavian SM. Liver complications in celiac disease. Hepatitis monthly. 2011; 11(5): 333.

[32] Vajro P, Fontanella A, Mayer M, De Vincenzo A, Terracciano LM, D'Armiento M, et al. Elevated serum aminotransferase activity as an early manifestation of gluten-sensitive enteropathy. The Journal of pediatrics. 1993; 122(3): 416-9.