

Case Series

Celiac Disease as a Cause of Malabsorption: A Clinic-Pathological Series of Five Cases

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Keywords

Gluten-sensitive enteropathy · Marsh-Oberhuber classification · Endoscopy · Histopathology

Abstract

Introduction: Celiac disease (CD) also called gluten-sensitive enteropathy is a noninfectious and an autoimmune cause of malabsorption. It can be difficult to diagnose because of wide range of gastrointestinal and extraintestinal symptoms. **Case Presentation:** Here, we present 5 cases of CD out of total 160 patients assessed for malabsorption at a tertiary care facility in western Maharashtra between 2022 and 2023. The male-to-female ratio was 1.5:1, and the age of patients ranged from 2 to 60. Chronic diarrhea was the most prevalent symptom, followed by weight loss and stomach pain. In each case, laboratory results showed elevated tissue transglutaminase IgA (tTG-IgA), along with varied levels of calcium and vitamin D deficiency. Two cases had normal endoscopic findings, one had whitish granular mucosa, while 2 cases had duodenal fold scalloping. Histopathological analysis verified the diagnosis, classifying the cases as Marsh types 3a, 3b, and 3c. There was no relationship between the severity of the histopathology and tTG-IgA levels. **Conclusion:** This case series of 5 cases takes into account the prevalence of CD as a cause of malabsorption in western India. It also emphasizes the significance of taking CD into account in patients with malabsorption and the necessity of following a multidisciplinary approach encompassing nutritional assessment, clinical evaluation, histopathology, and serology for an accurate diagnosis and course of treatment.

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Introduction

Celiac disease (CD), also called celiac sprue, is a gluten-sensitive enteropathy. It is an autoimmune and noninfective cause of malabsorption [1]. It is caused due to gliadin peptides in gluten-containing products like cereals such as wheat, rye, oats, and barley. The prevalence of CD is currently estimated to be around 1% worldwide, and it is becoming more and more prevalent even in regions of the world where CD was once considered to be insignificant [2]. A number of clinical reports from Iran, Turkey, and Israel indicated that the prevalence of CD in Asia was comparable to that in Europe [2]. Overall prevalence of CD in Asia is 1.8%. In China, 0.06% of people had CD autoimmunity, as shown by positive anti-transglutaminase IgA (tTG-IgA) and anti-DGP-IgG assay findings. Autoimmunity to CD was linked to female sex and wheat consumption. In north China's Shandong province, where wheat is a staple food, the prevalence was 0.76% [3].

Furthermore, a considerable incidence of CD has been extensively documented throughout the Indian subcontinent, particularly in areas where dietary gluten intake is strong, with demographic variation in the Indian population ranging from 0.3% in the southern part to 1.4% in the northern part [4]. Higher prevalence in the northern part has been attributed to staple wheat-based diet. Many studies are available in literature which have estimated the prevalence of CD in northern and southern regions of India, but our case series is one of those few studies that highlights the prevalence of CD in Western part of India.

CD presents with a wide variety of symptoms that can be intestinal and extraintestinal. Some of the digestive symptoms of CD are diarrhea, malabsorption, abdominal pain, bloating, vomiting, and weight loss. It can also cause extraintestinal manifestations like dermatitis herpetiformis, chronic fatigue, joint pain, anemia, migraines, depression, attention-deficit disorder, epilepsy, bone density problems, infertility, vitamin deficiencies, growth delays, delayed puberty, dental enamel problems, and other autoimmune conditions [5]. In addition to emphasizing the prevalence of CD in western India, this case series also emphasizes the variability in presentation, clinical and endoscopic findings in CD, thus leading to a missed diagnosis. Hence, knowledge of such variable findings remains crucial for early and definitive diagnosis by means of histopathology.

Case Description

Case 1

A 2-year-old female presented with abdominal pain. Laboratory investigations revealed a hemoglobin (Hb) level of 12.6 g/dL, mean corpuscular volume (MCV) of 80.6 fL, mean corpuscular hemoglobin (MCH) of 26.6 pg, and red cell distribution width (RDW) of 14.4%. The white blood cell (WBC) count was elevated at 15,600/ μ L, and the platelet count was significantly high at 511,000/ μ L. Vitamin D levels were low at 9 ng/mL, with serum calcium at 9.8 mg/dL. Iron studies showed serum iron of 68 μ g/dL, total iron-binding capacity (TIBC) of 140 μ g/dL, vitamin B12 of 167 pg/mL, and folate of 6.2 ng/mL. Endoscopy revealed scalloping of the duodenal folds (Fig. 1b) with a mosaic pattern and loss of villi. Histopathology showed subtotal villous atrophy (Fig. 2b), crypt hyperplasia, and an intraepithelial lymphocyte (IEL) count of 80 per 100 enterocytes (Fig. 2c). Immunohistochemistry CD 3 was performed which highlighted the IELs (Fig. 2d) consistent with Marsh classification type 3b. The anti-tTG-IgA level was >128, indicating a strong serological marker for CD.

Case 2

A 60-year-old female presented with chronic diarrhea. Her Hb was 10.5 g/dL, MCV was 72 fL, MCH was 25.1 pg, and RDW was 13.5%. The WBC count was 9,300/ μ L, and the platelet count was 178,000/ μ L. Vitamin D levels were slightly higher at 15 ng/mL, with serum calcium

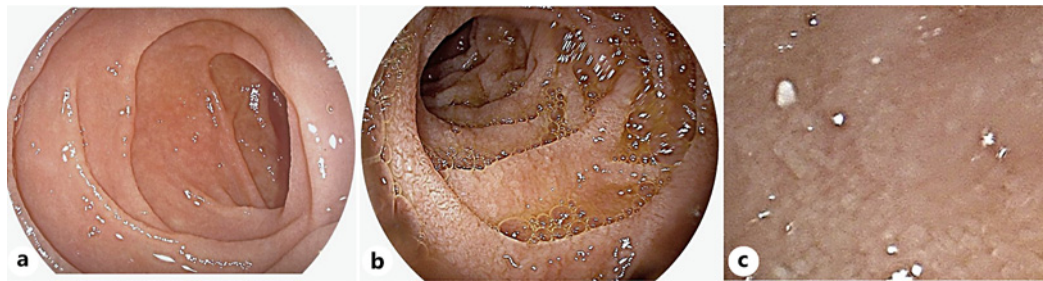


Fig. 1. Photo of endoscopy. **a** Normal mucosa in case 3 and case 5. **b** Scalloping of mucosa in case 1 and case 4. **c** Whitish granular mucosa seen in case 2.

at 8.6 mg/dL. Serum iron was low at 20 µg/dL, while TIBC was significantly elevated at 480 µg/dL. Vitamin B12 was 150 pg/mL, and folate levels were 60 ng/mL. Endoscopic findings included whitish-gray mucosa (Fig. 1c). Histopathology revealed total villous atrophy (Fig. 2a), crypt hyperplasia, and an IEL count of 40 per 100 enterocytes (Fig. 2c), categorized as Marsh type 3a. The anti-tTG-IgA level was 58.79, supporting a diagnosis of CD.

Case 3

A 36-year-old male presented with abdominal pain. His laboratory findings included a Hb of 15.1 g/dL, MCV of 87.5 fL, MCH of 30.4 pg, and RDW of 13.7%. The WBC count was 6,700/µL, and the platelet count was 25,200/µL. Vitamin D levels were 17 ng/mL, and serum calcium was 8.1 mg/dL. Serum iron was 62 µg/dL, with a TIBC of 270 µg/dL. Vitamin B12 and folate levels were 150 pg/mL and 2.3 ng/mL, respectively, indicating a folate deficiency. Endoscopy showed a normal study (Fig. 1a). However, histopathological examination revealed subtotal villous atrophy (Fig. 2b), absent crypt hyperplasia, and an IEL count of 50 per 100 enterocytes (Fig. 2c), categorized as Marsh type 3a. His anti-tTG-IgA level was 41.8, suggesting an immune response indicative of CD.

Case 4

A 26-year-old female presented with weight loss. Her Hb was low at 9 g/dL, with an MCV of 104.6 fL, MCH of 29.3 pg, and RDW of 14.4%. The WBC count was 15,600/µL, and the platelet count was significantly high at 5,11,000/µL. Vitamin D levels were low at 9 ng/mL, while serum calcium was 9.8 mg/dL. Serum iron was 68 µg/dL, and TIBC was 140 µg/dL. Vitamin B12 was 167 pg/mL, and folate levels were markedly low at 1.3 ng/mL. Endoscopic examination revealed scalloped duodenal folds (Fig. 1b). Histopathology demonstrated subtotal villous atrophy (Fig. 2b), crypt hyperplasia, and an IEL count of 40 per 100 enterocytes (Fig. 2c), categorized as Marsh type 3b. Her anti-tTG-IgA level was 35.73, supporting a diagnosis of CD.

Case 5

A 43-year-old male presented with abdominal pain and weight loss. His Hb level was 10.2 g/dL, with a high MCV of 117.2 fL, MCH of 31.3 pg, and RDW of 12.4%. The WBC count was 8,000/µL, and the platelet count was 356,000/µL. Vitamin D levels were low at 10 ng/mL, while serum calcium was 7.5 mg/dL. Serum iron was 50 µg/dL, and TIBC was elevated at 350 µg/dL. His vitamin B12 levels were significantly high (>2,000 pg/mL), while folate was critically low at 0.8 ng/mL. Endoscopy showed a normal study (Fig. 1a). However, histopathology demonstrated subtotal villous atrophy (Fig. 2b), crypt hyperplasia, and an IEL count of 60 per 100 enterocytes (Fig. 2c), categorized as Marsh type 3c. His anti-tTG-IgA level was markedly elevated at 284.71, indicating strong serological evidence of CD.

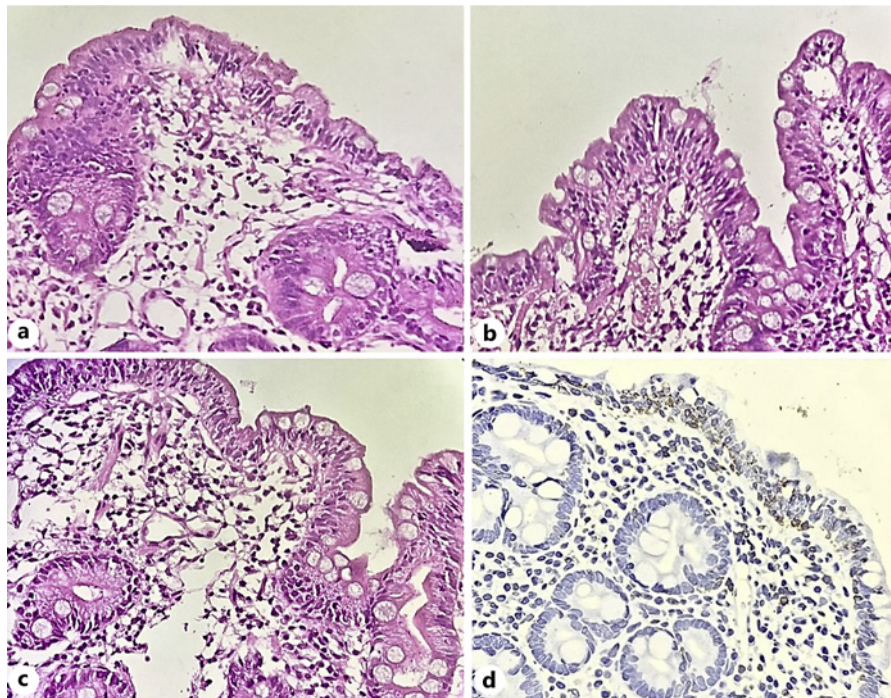


Fig. 2. **a** Photomicrograph showing total villous atrophy (H&E., ×400). **b** Subtotal villous atrophy (H&E., ×400). **c** Increased IEL (H&E., ×400). **d** IHC – CD 3 highlighting the increase in IEL.

Discussion

CD is a chronic, multi-organ autoimmune disorder affecting the small intestine in genetically predisposed individuals, triggered by gluten ingestion. It is also known as sprue, nontropical sprue, gluten-sensitive enteropathy, and gluten-induced enteropathy. The global prevalence of CD varies significantly, with regional differences observed in India as well [5]. However, data from western India, particularly Maharashtra, remain limited. Our case study found a prevalence of 3.12% in western Maharashtra, which may be attributed to migration patterns and changes in dietary habits. On comparing this case study with other studies in literature, the regional variations included the prevalence of CD to be 0.3% in the southern part and 1.4% in the northern part [4].

The development of CD involves a complex interplay of environmental, genetic, and immunological factors. Gluten, found in wheat, rye, and barley, is the primary environmental trigger. The proteins gliadin and glutenin in wheat, along with hordeins in barley and secalins in rye, contribute to disease activation. Genetically, the HLA DQA1 and DQB1 genes play a crucial role in presenting gluten peptides as antigens, making the MHC-HLA locus the most significant genetic determinant of CD. Immunologically, IELs contribute to epithelial damage after activation. Upon activation, T cells transform into a phenotype resembling natural killer cells, which mediate epithelial destruction by recognizing stress-induced molecules on the cell surface [1].

CD can be present at any age, from infancy to old age. According to Sahin et al. [5], there are two peaks in disease occurrence: one in early childhood (within 2 years of gluten introduction) and another in the second or third decade of life. Our study resembles this pattern, with cases spanning from pediatric to geriatric age groups. The disease is present with diverse symptoms, making diagnosis challenging. In children, common symptoms include diarrhea,

reduced appetite, abdominal bloating, weight loss, and growth failure [1]. Adults typically exhibit malabsorption syndrome, characterized by chronic diarrhea, steatorrhea, weight loss, and fatigue [4]. Atypical presentations include iron deficiency anemia, vitamin B12 and folic acid deficiencies, rickets in children, osteomalacia, osteoporosis, dental enamel defects, mouth ulcers, and dermatitis herpetiformis [6]. These varied presentations may result from multiple vitamin deficiencies and antibody-mediated duodenal mucosal damage caused by gluten peptides [6]. In our case series, the most common symptom was chronic diarrhea, followed by abdominal pain and weight loss.

CD frequently underlies hematological abnormalities, with anemia being the most common. In our study, Hb levels ranged from normal to abnormal. One patient had iron deficiency anemia, two had megaloblastic anemia, and two had normal Hb levels. Similar findings were reported by Therrien et al. [6]. The anemia in CD stems from impaired absorption of iron, folic acid, and vitamin B12. The etiology of vitamin B12 deficiency in CD is unclear but may involve reduced gastric acid secretion, bacterial overgrowth, autoimmune gastritis, or distal small intestinal dysfunction [7]. Iron deficiency primarily results from impaired intestinal iron absorption, although occult gastrointestinal bleeding may also contribute. Thrombocytopenia is rare in CD and may have an autoimmune basis. In our study, 1 patient had thrombocytopenia, and another had thrombocytosis. According to Halfdanarson et al. [7], thrombocytopenia in CD has been linked to keratoconjunctivitis and choroidopathy, suggesting an autoimmune etiology. Thrombocytosis is more common, affecting up to 60% of CD patients. Its cause is uncertain but may involve inflammatory mediators, iron deficiency anemia, or functional hyposplenism.

Gluten-induced immunological reactions damage the intestinal mucosa, leading to villous atrophy, crypt hyperplasia, and increased IELs. These changes impair nutrient absorption, particularly of calcium and vitamin D. Disruptions in vitamin D metabolism and calcium absorption contribute to bone imbalances, accelerating bone loss and turnover. In our study, 4 out of 5 patients had hypocalcemia, and all had vitamin D deficiency, consistent with findings from Dimitrios et al. [8].

Serological testing for IgA anti-tTG is highly sensitive and specific for CD. All 5 patients in our study had elevated anti-tTG levels. Pinkas et al. [9] proposed that the autoantibody response to tTG occurs even before histological changes develop. These antibodies are present in the intestinal mucosa and may enter the bloodstream before structural damage or mucosal lesions become evident, serving as an early diagnostic marker for CD. Other serological markers, including IgA gliadin antibodies and anti-endomysial antibodies, can also aid in diagnosis. Various serological tests detect CD with different levels of sensitivity and specificity. The tTG-IgA antibody test has a sensitivity of 92.5% and a specificity of 97.9%. Endomysial antibody IgA has a sensitivity of 79.0% and a specificity of 99.0%. Deamidated gliadin peptide antibody IgA has a sensitivity of 97% and a specificity of 90.7%. Deamidated gliadin peptide antibody IgG has a sensitivity of 95% and a specificity of 99.0% [10]. In our study, we analyzed tTG-IgA levels but found no direct correlation between tTG levels and histopathological findings.

Upper gastrointestinal endoscopy is a valuable tool in CD management. However, in our study, only 2 patients exhibited scalloping of the duodenal folds, the most common endoscopic finding in CD. One patient had a whitish granular mucosa, while two had normal findings, indicating that endoscopy alone is insufficient for diagnosis. Histopathological examination remains essential in cases of malabsorption, as supported by Enach et al. [11, 12]. Duodenal biopsy in all 5 cases showed subtotal or total villous atrophy, crypt hyperplasia, and an IEL count of more than 30 per 100 enterocytes. Based on the modified Marsh criteria, all cases were classified as Marsh type 3. These findings align with those of Meena et al. [13], who reported that most cases fell into the Marsh type 3 category. Villous atrophy in CD is linked to

enhanced apoptosis, and some studies suggest apoptosis plays a crucial role in CD pathogenesis [14].

The treatment of CD includes correcting nutritional deficiencies, preventing bone loss, managing dermatitis herpetiformis with sulfone therapy, maintaining a strict gluten-free diet, using transglutaminase-2 inhibitors, and receiving hepatitis B and pneumococcal vaccinations. According to M.J.J. Chris's postulate, follow-up for CD should include a physical examination, BMI assessment, and counseling by a dietitian specializing in CD at diagnosis. Family screening should also be suggested. Patients should be monitored every 3–4 months for symptom evaluation, adherence to a gluten-free diet, and IgA anti-tTG serology. At 12 months, a comprehensive assessment should include celiac serology, thyroid function tests, and metabolic evaluations. After 24 months, follow-ups should continue with symptom assessments and serological tests, with additional investigations as needed. As patients on gluten-free diet are at threefold increased risk to develop non-alcoholic fatty liver disease, an appropriate nutritional intake and proper follow-up with liver clinic are advised to reduce the risk of long-term liver-related events. [15]. Long-term monitoring should occur every 1–2 years, with bone densitometry performed in case of suspected abnormalities [16].

Conclusion

The prevalence of CD in India exhibits demographic variation. Contrary to the usual assumption/belief, the prevalence of CD in western India is 3% which is higher than northern and southern regions of India where wheat is the staple diet. This indicates that either very few cases of malabsorption seek treatment or remain underdiagnosed due to variability in presentation or poor follow-up. Migration of people and rice-based diet have also influenced the same.

CD can present at any age and may have a normal or variable endoscopic appearance, making diagnosis challenging. There is no direct correlation between serum tTG-IgA levels and the severity of histopathological findings. Patients with Marsh type 3 CD are more likely to have nutritional deficiencies, emphasizing the need for thorough screening.

Timely diagnosis remains a challenge for clinicians, as the disease often develops long before symptoms appear. The wide range of clinical presentations makes differential diagnosis difficult. In such cases, serological testing for anti-tTG is an effective screening tool. However, a definitive diagnosis requires a comprehensive approach, integrating serological, clinical, and histopathological findings. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online supplementary material, see <https://doi.org/10.1159/000545589>).

Limitations

Cost constraint, poor compliance with gluten-free diet, and loss to follow-up were the limiting factors in the study.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by institution ethics subcommittee of Dr. D.Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune – approval: IESC/441/2022. Written informed consent was obtained from all patients and parents/legal guardian of the minor patient for publication of the details of their medical case and accompanying images.

Conflict of Interest Statement

The authors declared no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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Author Contributions

Dr. Archana Chirag Buch and Dr. Tejaswini Rajesh Shrirao: conceptualization, data curation, formal analysis, investigation, methodology, validation, and writing – original draft, review, and editing; Dr. Mangesh Londhe: validation and review; Dr. Sargam Dhaliwal: data curation, formal analysis, methodology, and conclusion and references.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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