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Case Report

Giardia lamblia Mimicking Celiac Disease in an Immunocompromised Patient: A Case Report

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Abstract

Giardia lamblia infection can clinically and histopathologically mimic celiac disease. This challenge is particularly pronounced in immunocompromised patients, where serological tests may be negative and mucosal changes more exaggerated. A 52-year-old female with immunodeficiency presented with chronic diarrhea unresponsive to a gluten-free diet. Initial duodenal biopsies were reported as Marsh 3b, and celiac disease was considered in the first place despite negative serology. The first stool examination was negative for parasites. On repeat endoscopy, duodenal nodularity with intraepithelial lymphocytosis and nodular lymphoid hyperplasia was observed. Careful re-evaluation of biopsy slides and subsequent stool examination revealed *G. lamblia* trophozoites, confirming the diagnosis. Immunodeficiency complicated the diagnostic process by reducing antibody production, resulting in negative serology, and by allowing chronic infection to induce celiac-like mucosal alterations. Moreover, the initial false-negative stool test and elevated fecal calprotectin levels further suggested inflammatory bowel disease, adding to the diagnostic challenge. In patients with persistent symptoms despite adherence to a gluten-free diet, before diagnosing refractory celiac disease, parasitic agents particularly *G.lamblia* should be excluded in the first place. Repeated stool examinations and meticulous histopathological evaluation of duodenal biopsies are crucial for reaching the correct diagnosis.

Introduction

Celiac disease is a chronic autoimmune enteropathy characterized by villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes (IEL) in the small intestine, triggered by gluten intake in genetically predisposed individuals (1). Diagnosis is typically made through serological tests (anti-tTG, EMA) and small bowel biopsy.

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However, various conditions can mimic celiac disease and lead to similar histopathological findings, including infections, medications, and other autoimmune diseases (2). *Giardia lamblia* is a protozoan parasite widely distributed across the world. Clinical manifestations vary considerably, ranging from asymptomatic infection to chronic diarrhea and malabsorption. In the diagnosis of giardiasis, stool microscopy has traditionally been the primary method; however, due to the intermittent shedding of cysts, repeated examinations are often required. More sensitive approaches include stool antigen tests (e.g., ELISA), nucleic acid detection methods (PCR), and in some cases, endoscopic biopsies or examination of duodenal contents. Histopathologically, *Giardia* infection can lead to changes in the small intestine similar to celiac disease, including villous shortening, crypt hyperplasia, lamina propria inflammation, and increased IEL (3-6). The incidence is particularly high in developing countries due to poor sanitation and contaminated water supplies (7).

Although *Giardia* is not considered an opportunistic protozoan, intestinal infections are reported more frequently in immunocompromised individuals. In such patients, for example those with Common Variable Immunodeficiency (CVID), *G. lamblia* infection shows an increased tendency to cause enterocyte injury, subtotal villous atrophy, and the development of nodular mucosal patterns (8,9). Because CVID is associated with reduced antibody production, particularly diminished IgG and IgA levels, the ability to clear the parasite from the intestine is impaired (10). Its clinical impact can be more pronounced in immunocompromised patients, complicating the diagnostic process. Moreover, giardiasis may mimic other gastrointestinal disorders such as celiac disease, making the diagnostic process more complex in immunocompromised patients (9,10).

In addition, *Giardia* infection may also resemble inflammatory bowel disease (IBD). Elevated fecal calprotectin levels, a commonly used biomarker for IBD, have been reported in giardiasis, potentially leading to false positive results, misdiagnosis, or unnecessary further investigations (11).

In the treatment of giardiasis, the most commonly used drugs are metronidazole and tinidazole, while albendazole and nitazoxanide serve as alternative options (5).

Here we present a case in Turkey.

Case Presentation

A fifty-two-year-old female patient with a diagnosis of immunodeficiency presented to the Gastroenterology outpatient clinic with a long-standing complaint of watery diarrhea, occurring 4–5 times daily. Her medical history was notable for a red meat allergy. At the time of her initial admission, microscopic examination of stool samples for parasites was performed but yielded negative results. Fecal calprotectin level was measured as 135 μg/g in an external laboratory.

Four years earlier, the patient had undergone an upper gastrointestinal endoscopy with duodenal biopsies, which were reported as Marsh 3b. Based on these histologic findings and clinical symptoms, a diagnosis of celiac disease was presumed, and a strict gluten-free diet (GFD) was initiated. However, her symptoms persisted despite long-term adherence to GFD. Due to ongoing complaints and a suspicion of inflammatory bowel disease, a repeat endoscopy was performed. This revealed edema and nodularity in the duodenal mucosa (Fig. 1A). Histopathological examination of biopsy samples taken from the duodenum showed nodular lymphoid hyperplasia (NLH) in the lamina propria (Fig. 1B) and immunohistochemical CD3+ intraepithelial lymphocyte (IEL) increase (more than 30 IELs per 100 enterocytes) (Fig. 1C). Additionally, on conventional hematoxylin-eosin (H&E) staining, trophozoites of *G. lamblia* were identified within the duodenal mucosa. These parasites were observed as pear-shaped or oval structures on the villous surface and in the intervillous spaces (Fig. 1D). Moreover, stool exami-

nation at the last admission demonstrated *G. lamblia* trophozoites, confirming the diagnosis in correlation with the histopathological findings.

In order to definitively exclude seronegative celiac disease and considering the possibility that *Giardia* infection may have overlapped with celiac-like histopathological features, a retrospective review of the initial duodenal biopsy slides was performed. A retrospective review of the initial duodenal biopsy revealed the presence of a small number of *G. lamblia* trophozoites that had been initially overlooked. These retrospective findings confirmed the exclusion of seronegative celiac disease and indicated that the observed histopathological alterations were primarily attributable to *G. lamblia* infection.

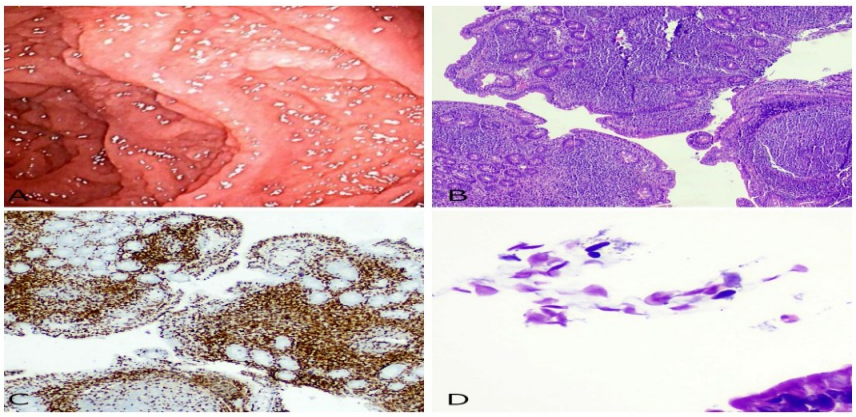

Fig. 1:(A) Endoscopic image showing mucosal nodularity in the second portion of the duodenum. (B) Histological section demonstrating nodular lymphoid hyperplasia in the lamina propria (Hematoxylin and eosin, original magnification ×100). (C) Immunohistochemical staining with CD3 showing increased intraepithelial lymphocytes (>30 IELs/100 enterocytes) (CD3, ×200). (D) Trophozoites of *Giardia lamblia* seen on the villous surface and in the intervillous space (Hematoxylin and eosin, ×400)

Discussion

The patient's clinical symptoms, the initial duodenal biopsy findings reported as Marsh 3b, the negative stool examination, and the absence of celiac serological markers initially raised the possibility of seronegative celiac disease. Celiac disease is an immune-mediated enteropathy triggered by gluten, characterized by villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes (IELs) (8).

However, *Giardia* infection may also produce similar histopathological features, making the distinction between these two conditions challenging (2). The role of CD8+ T cells in the pathogenesis of duodenal mucosal damage in *Giardia* infection is particularly noteworthy. *Giardia* triggers a host immune response that induces mucosal inflammation, during which CD8+ T lymphocytes become activated and contribute to epithelial alterations such as microvillus damage, disaccharidase deficiency, and malabsorption. In immunocompromised individuals, this response may be exaggerated, with more pronounced NLH and dense CD8+ lymphocyte infiltration. Importantly, the phenotypic profile of intraepithelial lymphocytes (IELs) can aid in the differential diagnosis between celiac disease and giardiasis. In celiac disease, increased IELs usually display an active cytotoxic phenotype, expressing both granzyme B and TIA-1, and thereby causing epithelial injury via granzyme B–mediated mechanisms. By contrast, in giardiasis, IELs are typically granzyme B–negative but TIA-1–positive, indicating a latent cytotoxic phenotype that is less likely to induce

direct epithelial damage (1,2). This immunohistochemical distinction may therefore serve as a valuable diagnostic clue in cases with negative celiac serology but increased IELs. In our case, granzyme B and TIA-1 immunostainings were not performed due to technical limitations; however, their diagnostic value has been emphasized in previous studies. In addition, the risk of missing *Giardia* parasites on conventional H&E staining can lead to diagnostic difficulties. Especially in cases with low parasite load or when morphological features are not distinct, Giardia trophozoites can be overlooked (6). Therefore, in suspected cases, C-kit (CD117) immunohistochemical staining is a valuable method that facilitates the diagnosis of *Giardia* and prevents it from being missed (6).

The nodular appearance observed during endoscopy may be consistent with NLH. NLH is characterized by lymphoid follicles rich in CD20+ B cells within the lamina propria and submucosa, and it is most commonly observed in the terminal ileum, less frequently in the jejunum and duodenum. The differential diagnosis should include celiac disease, Crohn's disease, infectious enterocolitis (particularly *G. lamblia*), immunodeficiency syndromes, intestinal lymphomas, and *Helicobacter pylori* infection. NLH is often seen in patients with antibody production defects, such as CVID, and may occur in association with chronic *Giardia* infection. In immunodeficient patients, this coexistence can produce villous atrophy and a nodular mucosal pattern, thereby closely mimicking celiac disease both clinically and histopathologically (1,8).

Fecal calprotectin is an important biomarker reflecting gastrointestinal inflammation and has high sensitivity and specificity in the diagnosis and follow-up of IBD. However, it is not specific to IBD; elevated levels may also be observed in infections (particularly *G. intestinalis*), celiac disease, NSAID-induced enteropathy, and colorectal neoplasms. In the literature, fecal calprotectin levels exceeding 2000 mg/kg have been reported in giardiasis cases, with rapid decline following treatment. In our case, the increase to 135 mg/kg initially raised suspicion of IBD; however, the diagnosis was confirmed by the demonstration of *Giardia* trophozoites in the duodenal biopsy and the subsequent detection of positivity in stool examination. Therefore, in cases with elevated fecal calprotectin, infectious causes must always be considered in the differential diagnosis (11).

Although stool microscopy is the standard method for the diagnosis of *Giardia* infection, false negatives may occur due to intermittent shedding of the parasite and its presence in low numbers. In our case, the negative result of the initial stool examination can be explained by these factors. More specific and sensitive methods, such as stool antigen ELISA, immunochromatographic assays, or PCR-based molecular tests, are superior to microscopy (5,6). However, they could not be performed as they were not available in our laboratory. At this point, histopathological evaluation played a critical role.

In patients whose symptoms persist despite adherence to a gluten-free diet, a diagnosis of refractory celiac disease should not be established without first carefully excluding all infectious and non-infectious causes of villous atrophy. These include infections (various viral, bacterial, and parasitic agents), drug-induced enteropathies, Crohn's disease, autoimmune enteropathies, allergic or ischemic colitis, colorectal neoplasms, and intestinal lymphomas (1,11). The differentiation of these conditions requires the combined evaluation of clinical, laboratory, and histopathological findings, which is of critical importance. To reach the correct diagnosis, a detailed clinical history, repetition of serological tests, repeated stool examinations, and careful re-evaluation of duodenal biopsies are essential (6,8).

Conclusion

This case demonstrates that *G. lamblia* infection can clinically and histopathologically mimic celiac disease, while the presence of immunodeficiency further amplifies the diagnostic challenges. Impaired antibody production and prolonged parasitic persistence may lead to negative serological results and accentuate celiac-like findings such as villous atrophy, intraepithelial lymphocytosis, and nodular lymphoid hyperplasia, thereby complicating the diagnostic process. In addition, false-negative stool examinations and elevated fecal calprotectin levels may suggest inflammatory bowel disease, further misleading clinical evaluation.

Therefore, in patients with persistent symptoms despite adherence to a gluten-free diet, before diagnosing refractory celiac disease, parasitic infections particularly *G. lamblia* should be excluded in the first place. Repeated stool examinations and meticulous histopathological evaluation of duodenal biopsies play a crucial role in reaching the correct diagnosis.

Ethical Approval

Written informed consent was obtained from the patient for publication of this case and accompanying images.

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Conflict of Interest

The authors declare no conflicts of interest.

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