ISSN: 2577 - 8005

Case Report

Medical & Clinical Research

Cryptogenic Hypertransaminasemia Unmasking Silent Celiac Disease: A Case Report

Domenico Cirillo[1], Vittoria Gammaldi[2*], Antonietta De Sena[2], Gianluigi Cuomo[2], Giuliana Vespere[3], Antonio Cozzolino[4], Vincenzo Nuzzo[2] and Paolo Tirelli[2]

[1]*Department of Clinical Medicine and Surgery, School of Specialization in Internal Medicine, University of Naples, Federico II, Naples, Italy*

[2]*Department of Internal Medicine, "Ospedale del Mare" Hospital, Naples, Italy*

[3]*Department of Gastroenterology and Endoscopy, "Ospedale del Mare", Hospital, Naples. Italy*

[4]*Gastroenterology and Endoscopy Unit, "Santa Maria delle Grazie" Hospital, Pozzuoli, Italy*

[*]Corresponding Author

Vittoria Gammaldi, MD, Department of Internal Medicine, "Ospedale del Mare" Hospital, Via E. Russo, 11, 80147 Naples, Italy.

Submitted: 28 Oct 2025; **Accepted**: 05 Dec 2025; **Published**: 23 Dec 2025

Citation: Cirillo, D., Gammaldi, V., De Sena, A., Cuomo, G., Vespere, G., et al. (2025). Cryptogenic Hypertransaminasemia Unmasking Silent Celiac Disease: A Case Report. *Med Clin Res, 10*(12), 01-05.

Abstract

Celiac hepatitis represents an underestimated cause of unexplained liver enzyme elevation, affecting approximately twenty-one percent of patients with celiac disease. We report the case of a fifty-year-old man presenting with persistent isolated hypertransaminasemia and nonspecific fatigue. After excluding common causes of liver dysfunction including viral hepatitis, autoimmune and metabolic liver diseases, celiac disease screening revealed markedly elevated anti-tissue transglutaminase IgA antibodies. Duodenal biopsy confirmed Marsh grade 3 villous atrophy, establishing the diagnosis. Complete normalization of transaminase levels occurred within three months of strict gluten-free diet adherence. This case underscores the importance of maintaining high diagnostic suspicion for celiac disease in patients with cryptogenic hypertransaminasemia, given the excellent therapeutic response to dietary intervention and the substantial underdiagnosis of this treatable condition in clinical practice.

Keywords: Celiac disease, Celiac hepatitis, Hypertransaminasemia, Gluten-free diet, Extraintestinal features

1. Introduction

Celiac disease affects approximately one percent of the general population and represents a systemic autoimmune disorder triggered by gluten ingestion in genetically predisposed individuals [1]. While classically characterized by gastrointestinal manifestations, the disease frequently presents with extraintestinal features that may overshadow typical digestive symptoms. Among these atypical presentations, liver involvement constitutes a particularly relevant but frequently overlooked clinical scenario.

Celiac hepatitis manifests as elevated liver enzymes in the absence of other identifiable hepatic pathology and affects approximately twenty-one percent of patients with celiac disease [2]. The condition typically presents as asymptomatic or minimally symptomatic elevation of aminotransferases, representing a diagnostic challenge in routine clinical practice [3]. The pathophysiological mechanisms underlying hepatic involvement are multifactorial and include gluten-induced compromise of intestinal barrier function with subsequent translocation of inflammatory mediators via portal circulation, direct immunological injury mediated by tissue transglutaminase antibodies, and gut microbiota dysbiosis contributing to metabolic dysregulation [4-6].

Despite documented associations between celiac disease and liver dysfunction, the condition continues to be substantially underdiagnosed. Large-scale studies have demonstrated that nearly half of celiac disease patients present with abnormal liver function tests at diagnosis, yet systematic screening for celiac disease in patients with unexplained hypertransaminasemia remains inconsistently implemented [8]. This case report illustrates the diagnostic challenge posed by celiac hepatitis and emphasizes the therapeutic implications of this frequently missed condition.

2. Case Report

A fifty-year-old Caucasian man was referred for evaluation of persistent elevation of liver enzymes. The patient reported several months of nonspecific general fatigue but denied gastrointestinal symptoms including abdominal pain, diarrhea, bloating, or weight changes. His past medical history was unremarkable except for a liver biopsy performed twenty years earlier for unclear reasons.

Physical examination revealed no significant abnormalities, with no stigmata of chronic liver disease. Initial laboratory evaluation confirmed elevated alanine aminotransferase at 226 U/L and aspartate aminotransferase at 118 U/L. Other liver function parameters including bilirubin, alkaline phosphatase, gamma-glutamyl transferase, albumin, and prothrombin time remained within normal limits. Complete blood count showed mild microcytic anemia.

Comprehensive diagnostic workup was initiated. Viral hepatitis screening including hepatitis B surface antigen, hepatitis B core antibodies, and hepatitis C antibodies returned negative results. Autoimmune liver disease evaluation revealed weakly positive antinuclear antibodies at 1:80 with homogeneous pattern, while anti-smooth muscle antibodies, anti-liver-kidney microsomal antibodies, and anti-mitochondrial antibodies were negative. Metabolic screening demonstrated normal ceruloplasmin and alpha-1 antitrypsin levels. Iron studies showed normal transferrin saturation with ferritin of 18 ng/mL, consistent with mild iron deficiency.

Abdominal ultrasound examination revealed normal liver echotexture without steatosis or cirrhosis. Two small hepatic focal lesions measuring 8 and 12 millimeters with characteristics consistent with benign hemangiomas were identified.

Given persistent unexplained hypertransaminasemia despite extensive negative workup, celiac disease screening was pursued. Anti-tissue transglutaminase IgA antibodies were markedly elevated at 126 IU/L, with normal total IgA levels excluding selective IgA deficiency. Upper endoscopy revealed subtle duodenal mucosal changes including scalloping and mosaic pattern (**Figure 1**). Histopathological examination of duodenal biopsies demonstrated villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes consistent with Marsh grade 3 classification, confirming celiac disease.

The patient received comprehensive counseling regarding strict lifelong adherence to gluten-free diet and was referred to a clinical nutritionist for detailed dietary education. After three months of rigorous gluten elimination, repeat laboratory evaluation demonstrated complete normalization of liver enzyme levels, with alanine aminotransferase at 28 U/L and aspartate aminotransferase at 31 U/L. Anti-tissue transglutaminase IgA antibodies decreased to 42 IU/L. The patient reported significant improvement in energy levels, confirming celiac hepatitis and validating the therapeutic response.

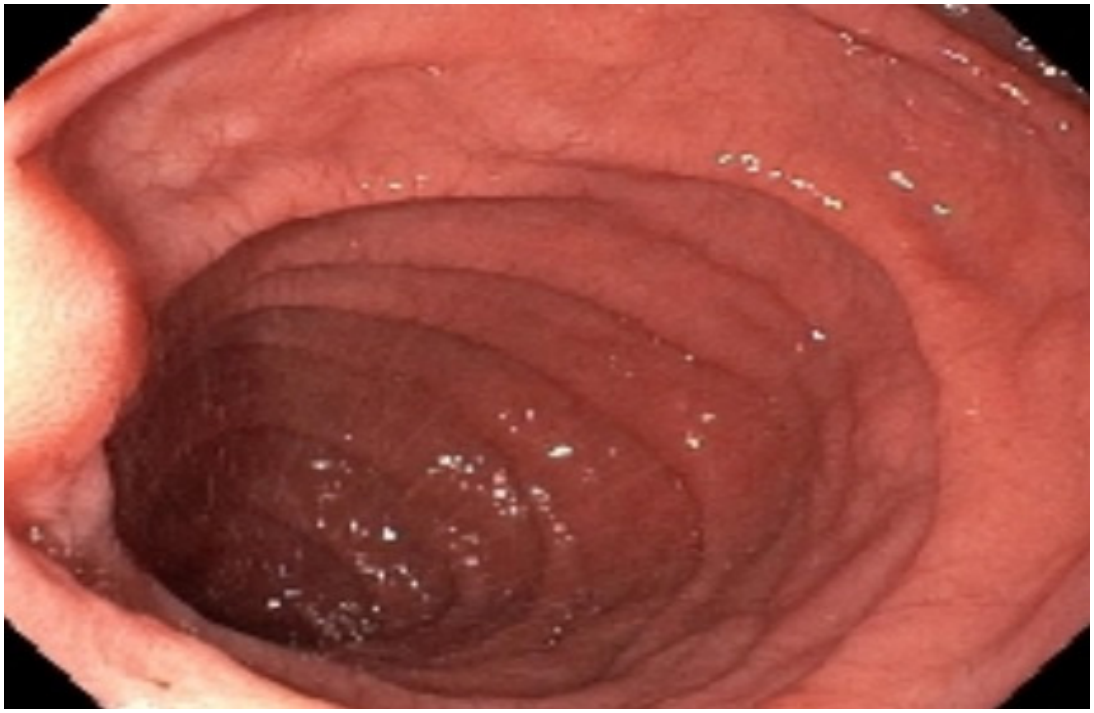

Figure 1: Upper endoscopy showing duodenal mucosal changes characteristic of celiac disease, including scalloping pattern and mosaic appearance of the mucosa.

3. Discussion

This case exemplifies the clinical challenge posed by celiac hepatitis, affecting nearly one in five patients with celiac disease yet remaining significantly underdiagnosed [2]. The presentation of isolated hypertransaminasemia without obvious gastrointestinal symptoms requires heightened diagnostic suspicion for celiac disease, particularly after excluding more common etiologies [3].

The diagnostic approach followed a systematic algorithm for evaluating unexplained hypertransaminasemia. Initial evaluation appropriately excluded viral hepatitis, autoimmune liver diseases, and metabolic disorders. The presence of weakly positive antinuclear antibodies presented a consideration, as the association between celiac disease and autoimmune hepatitis is well documented. Recent systematic reviews demonstrate significantly higher celiac disease prevalence in patients with autoimmune hepatitis, supporting routine bidirectional screening [8]. However, the absence of other autoimmune markers and complete normalization with gluten-free diet alone confirmed that hepatic involvement was primarily celiac-related.

The markedly elevated anti-tissue transglutaminase IgA antibody level of 126 IU/L is consistent with epidemiological data demonstrating that celiac disease patients with abnormal liver function tests exhibit significantly higher antibody titers compared to those with normal liver profiles. A Portuguese cohort study reported median antibody levels of 126 IU/L in patients with liver abnormalities versus 29 IU/L in those with normal profiles, suggesting higher titers indicate more extensive immune activation and greater likelihood of extraintestinal manifestations [7,9].

The pathophysiological mechanisms involve multiple interconnected processes. Gluten-induced compromise of intestinal barrier function leads to increased permeability through zonulin release and disruption of tight junction proteins, facilitating translocation of inflammatory mediators to the hepatic circulation via portal system. Additionally, tissue transglutaminase IgA antibodies identified in hepatic tissue suggest direct immunological injury [4,5]. Gut microbiota dysbiosis, characterized by altered microbial communities with increased Firmicutes and Proteobacteria, activates toll-like receptor pathways and inflammasome responses, contributing to hepatic inflammation and metabolic dysregulation [6].

The differential diagnosis requires careful consideration of both celiac-specific hepatitis and concurrent liver pathologies. Meta-analytical data reveals celiac hepatitis represents approximately forty-nine percent of cases, while other etiologies include autoimmune hepatitis, viral hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and non-alcoholic fatty liver disease [2]. This broad differential underscores the importance of comprehensive evaluation.

The therapeutic response with complete normalization within three months aligns with published evidence demonstrating response rates of approximately eighty-six percent [2]. Approximately sixty-five percent of patients achieve normal transaminase levels within one year and seventy-seven percent within two years [7]. The dramatic response confirms that isolated dietary intervention suffices for most cases without requiring hepatoprotective medications or immunosuppressive therapy.

Long-term studies provide reassuring evidence regarding prognosis. A Portuguese study with median follow-up of nine years demonstrated excellent outcomes without progression to chronic liver disease, advanced fibrosis, or cirrhosis [7]. However, approximately forty-three percent developed hepatic steatosis during follow-up, potentially related to the hyperlipidemic and hypercaloric nature of many commercially available gluten-free products [7]. This emphasizes the critical importance of comprehensive nutritional counseling extending beyond simple gluten elimination.

Several clinical implications emerge from this case. Celiac disease screening should be systematically considered in patients with unexplained hypertransaminasemia, even without gastrointestinal symptoms [3]. **Figure 2** illustrates a practical diagnostic algorithm incorporating celiac disease screening into the systematic evaluation of cryptogenic hypertransaminasemia. The excellent therapeutic response and favorable long-term prognosis reinforce the importance of early diagnosis to avoid unnecessary invasive procedures or inappropriate therapies. Long-term multidisciplinary follow-up remains essential to monitor dietary compliance, assess for metabolic complications including hepatic steatosis, and identify concurrent liver pathologies requiring additional intervention.

Take-home message: Celiac disease should be systematically considered in unexplained hypertransaminasemia, even without gastrointestinal symptoms. The condition responds excellently to gluten-free diet alone but requires long-term multidisciplinary follow-up to prevent metabolic complications and ensure sustained dietary compliance.

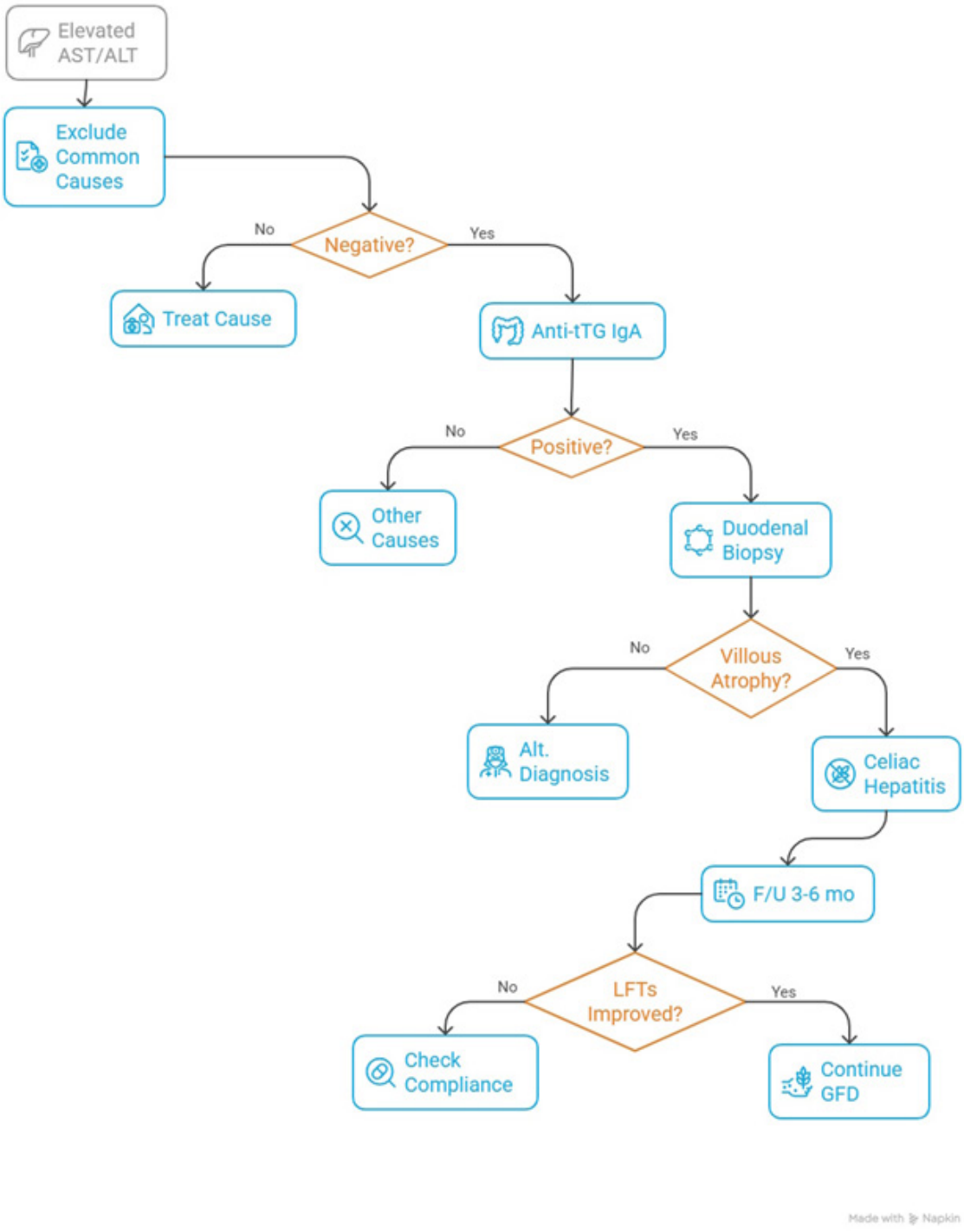

Figure 2: Diagnostic algorithm for the evaluation of unexplained hypertransaminasemia with systematic integration of celiac disease screening. AST: aspartate aminotransferase; ALT: alanine aminotransferase; Anti-tTG IgA: anti-tissue transglutaminase IgA antibodies; GFD: gluten-free diet; F/U: follow-up, LFTs. Liver function tests.

4. Conclusion

Celiac hepatitis represents a clinically significant but frequently underrecognized cause of hypertransaminasemia affecting approximately one in five patients with celiac disease [2]. This case demonstrates that the condition often presents with subtle clinical manifestations requiring high diagnostic suspicion and systematic screening approaches [3]. The dramatic normalization achieved through strict dietary intervention alone underscores the

excellent therapeutic efficacy of gluten-free diet in this condition. Healthcare providers must maintain heightened awareness of celiac disease as a potential etiology in patients with cryptogenic liver enzyme elevation. Systematic integration of celiac disease screening into diagnostic algorithms could significantly reduce diagnostic delays and prevent unnecessary invasive procedures. While gluten-free diet provides highly effective treatment with excellent long-term prognosis, comprehensive patient management requires ongoing multidisciplinary care involving gastroenterologists, clinical nutritionists, and internists to address both the underlying celiac disease and potential long-term complications, particularly hepatic steatosis related to suboptimal nutritional quality of commercially available gluten-free products [7]. This integrated approach optimizes long-term outcomes and quality of life for patients affected by this treatable cause of liver dysfunction.

Conflict of Interest Statement

The authors declare no conflict of interest.

Author Contributions

D.C, P.T. and V.G conceived the study and drafted the manuscript. P.T., D.C., G.C., A.D.S., A.C., V.G. G.V. and V.N. collected and interpreted clinical data. All authors approved the final version.

Funding

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical Approval of Studies and Informed Consent

The study followed the principles of the Declaration of Helsinki as revised in 2013. According to the guideline of the Ethics Committee of "Ospedale del Mare" Hospital, publication of single case reports is exempt from formal ethics approval. Written informed consent for publication was obtained from the patient. The patient also provided specific written consent for the publication of anonymized clinical images.

References

1. Caio, G., Volta, U., Sapone, A., Leffler, D. A., De Giorgio, R., Catassi, C., & Fasano, A. (2019). Celiac disease: a comprehensive current review. *BMC medicine, 17*(1), 142.
2. Jena, A., Kumar-M, P., Kumar, A., Birda, C. L., Choudhury, A., Kumar, N., ... & Samanta, J. (2023). Liver abnormalities in celiac disease and response to gluten free diet: A systematic review and meta-analysis. *Journal of Gastroenterology and Hepatology, 38*(1), 11-22.
3. Kim, J. V., & Wu, G. Y. (2020). Celiac disease and elevated liver enzymes: a review. *Journal of clinical and translational hepatology, 9*(1), 116.
4. Lammers, K. M., Lu, R., Brownley, J., Lu, B., Gerard, C., Thomas, K., ... & Fasano, A. (2008). Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. *Gastroenterology, 135*(1), 194-204.
5. Korponay-Szabó, I. R., Halttunen, T., Szalai, Z., Laurila, K., Király, R., Kovács, J. B., ... & Mäki, M. (2004). In vivo targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. *Gut, 53*(5), 641-648.
6. Verdu, E. F., Galipeau, H. J., & Jabri, B. (2015). Novel players in coeliac disease pathogenesis: role of the gut microbiota. *Nature Reviews Gastroenterology & Hepatology, 12*(9), 497-506.
7. Garrido, I., Liberal, R., Peixoto, A., & Macedo, G. (2022). Long-term follow-up and prognosis of celiac hepatitis. *European Journal of Gastroenterology & Hepatology, 34*(12), 1255-1260.
8. Haggård, L., Glimberg, I., Lebwohl, B., Sharma, R., Verna, E. C., Green, P. H., & Ludvigsson, J. F. (2021). High prevalence of celiac disease in autoimmune hepatitis: Systematic review and meta-analysis. *Liver International, 41*(11), 2693-2702.
9. Nurminen, S., Kivelä, L., Huhtala, H., Kaukinen, K., & Kurppa, K. (2019). Extraintestinal manifestations were common in children with coeliac disease and were more prevalent in patients with more severe clinical and histological presentation. *Acta Paediatrica, 108*(4), 681-687.