



CASE REPORT

Seronegative celiac disease with transient protein-losing enteropathy and vitamin B12 deficiency in a pediatric patient: Case report

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Key Clinical Message

Early recognition and management of seronegative celiac disease, even in the absence of typical serological markers, can prevent complications and ensure better health outcomes in pediatric patients. Consideration of a gluten-free diet in similar cases can lead to significant clinical improvement.

Abstract

Celiac disease, characterized by its diverse clinical manifestations, often necessitates adherence to a gluten-free diet, particularly in pediatric patients for optimal growth and development. This report presents the case of an 11-year-old male who exhibited recurrent symptoms of fever and diarrhea progressing to edema and pallor, with a history dating back to age 3. Laboratory findings revealed pancytopenia, hypoalbuminemia, and proteinuria. Despite negative serological markers, noninvasive tests, along with clinical improvement on a gluten-free diet and supportive measures within a month, suggested celiac disease complicated by transient protein-losing enteropathy and vitamin B12 deficiency. It is important to note that other malabsorption disorders can also show clinical improvement following a gluten-free diet. Additionally, the antibiotic treatment received by the patient could have addressed other possible causes of malabsorption, complicating the differential diagnosis. This case highlights the importance of early recognition and management of celiac disease, especially in pediatric patients, to prevent complications and promote optimal health outcomes.

KEYWORDS

chronic diseases, endocrinology and metabolic disorders, gastroenterology/hepatology, immunology, pathology and laboratory medicine

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1 | INTRODUCTION

Celiac disease is a chronic autoimmune disorder characterized by an inappropriate immune response to ingested gluten, a protein found in wheat, barley, and rye. This response leads to inflammation and damage to the small intestine's mucosa, impairing nutrient absorption. The global prevalence of celiac disease is approximately 1.4% based on serological testing and 0.7% based on biopsy-confirmed case.¹

Typically diagnosed in childhood, celiac disease can present with a wide range of gastrointestinal and extraintestinal symptoms. Common gastrointestinal symptoms include chronic diarrhea, abdominal pain, and bloating, while extraintestinal manifestations may involve anemia, osteoporosis, dermatitis herpetiformis, and neurological symptoms.² Diagnosis is often confirmed through serological tests for antibodies such as anti-tissue transglutaminase (TTG) and anti-endomysial antibodies (EMA), followed by a confirmatory biopsy showing villous atrophy and crypt hyperplasia in the small intestine. However, a subset of patients presents with seronegative celiac disease, where typical serological markers are absent, and diagnosis may require genetic testing (HLA-DQ2/DQ8) and a trial of a gluten-free diet.³

However, a subset of patients presents with seronegative celiac disease, where typical serological markers are absent despite clinical and histological evidence of the disease. Seronegative celiac disease can pose significant diagnostic challenges, as it may be misdiagnosed or overlooked. It affects approximately 3%–5% of individuals with celiac disease and often requires more invasive diagnostic approaches, including genetic testing for HLA-DQ2/DQ8 and a trial of a gluten-free diet.³

This case report highlights an 11-year-old boy with seronegative celiac disease presenting with atypical features, including transient protein-losing enteropathy and vitamin B12 deficiency. The patient's presentation underscores the importance of considering celiac disease in the differential diagnosis of pediatric patients with unexplained gastrointestinal and systemic symptoms, even in the absence of positive serological markers. This case also emphasizes the need for a comprehensive diagnostic approach and the benefits of early intervention with a gluten-free diet to improve patient outcomes.

2 | CASE HISTORY/ EXAMINATION

An 11-year-old boy, weighing 30 kg and measuring 132 cm (below the 3rd centile), initially presented with fever and diarrhea 15 days prior. He was prescribed metronidazole

for 3 days, which provided temporary relief, but the treatment was discontinued by his family. Five days later, he developed progressive body swelling starting from his feet, followed by generalized edema, progressive pallor, and rapid breathing, prompting medical attention. On examination, he displayed signs of anemia, including generalized pitting edema, grade 1 clubbing, hepatomegaly (spanning 14 cm), a 3 cm spleen below left costal margin, and ascites. There were no prominent vessels, jaundice, cutaneous manifestations, or history of chronic diarrhea noted. Interestingly, he had a similar illness at the age of 3, marked by diarrhea and mild edema, which resolved with treatment within 10 days. Following an immediate blood transfusion, the patient underwent comprehensive investigations to examine potential infectious and atypical manifestations of different conditions. This included exploring possibilities such as hemolytic uremic syndrome (HUS), autoimmune disorders, chronic malnutrition, and malignancy, as no single diagnosis was evident.

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

Laboratory tests revealed pancytopenia (Hemoglobin [Hb] 5.2 g/dL, total leukocyte count [TLC] $2.8 \times 10^3/\mu\text{L}$, absolute neutrophilic count $1200/\mu\text{L}$, platelet count [PLT] $86 \times 10^3/\mu\text{L}$) with eosinophilia (13%) and a reticulocyte count of 0.2% (Table 1). Cultures for infections and tests for malaria and dengue returned negative results, while

TABLE 1 Laboratory results of the patient at initial presentation.

Parameter	Result	Normal Range
Hemoglobin (Hb)	5.2 g/dL	13.5–17.5 g/dL
Total Leukocyte Count (TLC)	$2.8 \times 10^3/\mu\text{L}$	$4.0\text{--}11.0 \times 10^3/\mu\text{L}$
Absolute Neutrophil Count (ANC)	$1200/\mu\text{L}$	$1500\text{--}8000/\mu\text{L}$
Platelets (PLT)	$86 \times 10^3/\mu\text{L}$	$150\text{--}450 \times 10^3/\mu\text{L}$
Eosinophils	13%	1%–4%
Reticulocyte Count	0.2%	0.5%–2.5%
Serum Albumin	1.2 g/dL	3.5–5.0 g/dL
Vitamin B12	153 pg/mL	200–900 pg/mL
ANA	8	6–10 index
Anti-dsDNA	6	10–15 IU/mL
Direct Coombs	1	0–4 IU/mL
C3 Level	0.6 g/L	0.9–1.8 g/L
Anti-TTG Ab (IgA)	Negative	Negative
HLA-DQ2	Positive	Negative

urine analysis showed initial proteinuria (+3), negative leukocytes, and positive nitrites. Although there were no active loose stools, stool microscopy revealed the presence of *Entamoeba histolytica*. Additionally, the patient exhibited low levels of Vitamin B12 (153 pg/mL) and serum albumin (1.2 g/dL) (Table 1). Further investigations for HUS and autoimmune disorders including direct Coombs test antinuclear antibody and Anti-dsDNA were negative except for hypocomplementemia (C3 level of 0.6 g/L) (Table 1). After treating a urinary tract infection, a urine analysis revealed trace amounts of protein. Pediatric nephrology consultation excluded renal pathology but opted against performing a renal biopsy, recommending further investigation into other potential causes.

We conducted screening for celiac disease by assessing serum IgA and Anti-TTG Ab levels, which yielded normal results. Consequently, we contemplated performing a gastrointestinal biopsy to investigate potential causes of malabsorption. Unfortunately, the patient's parents declined to provide consent for the procedure. Initial tests for malabsorption, such as stool globules and calprotectin levels, showed no abnormalities except for reducing sugars, which normalized after treatment was discontinued. In addition to this immunogenetic testing were positive for HLA-DQ2. Following the completion of treatment for *Entamoeba histolytica* using Oral diloxanide + metronidazole, alpha-1 antitrypsin levels were assessed. Despite normal levels, clinical concern persisted regarding gut infection-induced gut injury and transient protein-losing enteropathy, which were observed during the current episode and at the age of 3.

4 | OUTCOME AND FOLLOW-UP

After initiating a gluten-free diet and providing supportive measures, the patient showed significant improvement within a month. The edema subsided, and his overall health and energy levels improved. Over the next year, the patient was closely monitored through regular follow-up visits every 3 months.

During these visits, the patient continued to adhere to a strict gluten-free diet. His growth parameters showed steady improvement, with a weight increase to 36 kg and a height of 140 cm, moving him closer to the 10th centile. Laboratory tests revealed normalized Hb levels (13 g/dL), TLC ($6.5 \times 10^3/\mu\text{L}$), and PLT ($250 \times 10^3/\mu\text{L}$). Serum albumin levels also improved to 4.0 g/dL, and vitamin B12 levels returned to the normal range (350 pg/mL) (Table 2).

The patient experienced no further episodes of edema or significant gastrointestinal symptoms. His quality of life markedly improved, with better school attendance and participation in physical activities. The case demonstrates the

TABLE 2 Follow-up laboratory results after 1 year.

Parameter	Result	Normal Range
Hemoglobin (Hb)	13 g/dL	13.5–17.5 g/dL
Total leukocyte count (TLC)	$6.5 \times 10^3/\mu\text{L}$	$4.0\text{--}11.0 \times 10^3/\mu\text{L}$
Platelets (PLT)	$250 \times 10^3/\mu\text{L}$	$150\text{--}450 \times 10^3/\mu\text{L}$
Serum Albumin	4.0 g/dL	3.5–5.0 g/dL
Vitamin B12	350 pg/mL	200–900 pg/mL

effectiveness of a gluten-free diet in managing seronegative celiac disease and highlights the importance of long-term follow-up to ensure sustained improvement and growth.

5 | DISCUSSION

This might be the first documented instance of Seronegative Celiac disease accompanied by a deficiency in vitamin B12 along with transient protein loss. Often, this condition is mistaken for irritable bowel syndrome (IBS) or goes unnoticed.³ Seronegative Celiac disease affects about 3%–5% of individuals who test negative for certain antibodies. The lack of these antibodies could be due to an IgA deficiency, leading to negative results in tests like IgA TTG and EMA.[3] Patients suspected of having celiac disease but testing negative for typical antibodies should have their total IgA levels checked, along with antibodies like anti-tissue transglutaminase, anti-deamidated gliadin peptide, and endomysial antibody (IgA).⁴

Seronegative celiac disease necessitates thorough evaluation, including -DQ2/8 testing and observing the response to a gluten-free diet, following the exclusion of other potential causes of seronegative villous atrophy.⁵ An earlier study found that most patients with villous atrophy have Seronegative celiac disease.⁶ Thus, it would have been advantageous to undertake both a pernicious anemia workup and a GI biopsy, which is the limitation of our case report. Furthermore, the presence of pancytopenia caused by either vitamin B12 deficiency or amebiasis could not explain how the edema developed. Instead, it is more probable that the edema was caused by protein loss after gastrointestinal and urinary infections.⁷

Nonetheless, since the urinary tract infection did not cause significant proteinuria, our predominant suspicion for the generalized edema moved to protein-losing enteropathy.⁸

6 | CONCLUSION

This case report highlights the complexities of diagnosing seronegative celiac disease, particularly in the absence of

positive serological markers and a confirmatory duodenal biopsy. The clinical improvement following a gluten-free diet, while suggestive of celiac disease, does not rule out other malabsorption disorders that may also respond to dietary changes. Additionally, the antibiotic treatment received could have treated infections or other conditions that may have contributed to malabsorption, thereby complicating the differential diagnosis. Our report emphasizes the importance of a thorough and comprehensive approach in diagnosing seronegative celiac disease, which may include genetic testing and careful monitoring of the patient's response to a gluten-free diet. Further research is needed to improve comprehension and management of similar presentations.

AUTHOR CONTRIBUTIONS

Aisha Shaikh: Conceptualization; data curation; validation. **Saad Ashraf:** Validation; visualization; writing – review and editing. **Muhammad Ahsan Ansari:** Data curation; resources; software. **Muhammad Zain-Ul-Haq:** Investigation; project administration; visualization. **Hashim Talib Hashim:** Funding acquisition; methodology; validation. **Ali Talib Hashim:** Conceptualization; software; supervision. **Ahmed Qasim Mohammed Alhatemi:** Project administration; writing – review and editing.

FUNDING INFORMATION

No sources of funding were received.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT


The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Shaikh A, Ashraf S, Ansari MA, et al. Seronegative celiac disease with transient protein-losing enteropathy and vitamin B12 deficiency in a pediatric patient: Case report. *Clin Case Rep.* 2024;12:e9297. doi:[10.1002/ccr3.9297](https://doi.org/10.1002/ccr3.9297)