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# Celiac Disease-Associated Protein-Losing Enteropathy Presenting as Refractory Hypogammaglobulinemia

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## Abstract

Protein-losing enteropathy (PLE) is a syndrome of nonselective enteric loss of plasma proteins, including albumin and immunoglobulins, in the absence of hepatic or renal disease. We describe a 30-year-old man with a remote, untreated diagnosis of hypogammaglobulinemia whose immunoglobulin G (IgG) remained profoundly low despite adequately dosed intravenous and then subcutaneous immunoglobulin replacement over a period of years. An elevated stool alpha-1-antitrypsin prompted gastroenterology referral. Despite ongoing gluten consumption and no gastrointestinal symptoms, he was diagnosed with celiac disease complicated by PLE, based on duodenal histology, positive tissue transglutaminase immunoglobulin A (IgA) serology, and a compatible HLA-DQ genotype. After starting a strict gluten-free diet, serum IgG and albumin improved, and immunoglobulin replacement was discontinued. This case highlights celiac disease as a treatable, potentially reversible cause of hypogammaglobulinemia that should be considered before attributing refractory low IgG to a primary immunodeficiency, and it underscores the value of fecal alpha-1-antitrypsin when immunoglobulin replacement fails to raise serum IgG.

**Categories:** Internal Medicine, Allergy/Immunology, Gastroenterology
**Keywords:** celiac disease, hypogammaglobulinemia, primary immune deficiency, protein-losing enteropathy, secondary immune deficiency

## Introduction

Hypogammaglobulinemia is frequently attributed to primary immunodeficiency, but a wide range of secondary and treatable causes must be excluded before a primary diagnosis is made [1]. Protein-losing enteropathy (PLE) is one such cause. PLE is a syndrome, not a disease, defined by uncompensated loss of plasma proteins into the intestinal lumen, identified by elevated stool alpha-1-antitrypsin >1.13 mg/g (reference range: 0-0.50 mg/g), leading to panhypoproteinemia in the absence of liver or kidney disease [2]. Because the loss is nonselective, both albumin and immunoglobulins are depleted, and infection can result from the ensuing hypogammaglobulinemia [2]. Other causes of PLE include inflammatory bowel disease, infections, peptic ulcer disease, intestinal lymphangiectasia, and malignancy. Common variable immunodeficiency (CVID) can also cause protein loss through impaired B-cell function at the mucosal surface.

Celiac disease, an immune-mediated enteropathy triggered by dietary gluten in genetically susceptible individuals, is frequently associated with PLE, with the degree of protein loss correlating with the severity of villous architectural abnormality and responding to a gluten-free diet [2,3]. Celiac disease has also been reported as a cause of profound, yet sometimes asymptomatic, reversible hypogammaglobulinemia, and routine celiac serology may itself uncover underlying immunoglobulin A (IgA) deficiency and broader antibody deficiency [4,5]. We present a case in which celiac disease-associated PLE was identified only after immunoglobulin replacement repeatedly failed to normalize serum immunoglobulin G (IgG).

## Case Presentation

A 30-year-old man with a history of seasonal allergies, urticaria, and a remote, untreated diagnosis of hypogammaglobulinemia presented to an allergy/immunology clinic for evaluation of environmental allergies. During the visit, he also reported easy fatigability and a tendency toward lingering infections, prompting reassessment of his known hypogammaglobulinemia.

Basic immune evaluation revealed a markedly low serum IgG of 204 mg/dL (reference range: 726-1521 mg/dL), a low IgA of 54 mg/dL (reference range: 87-426 mg/dL), and a normal immunoglobulin M (IgM). Functional antibody testing demonstrated subprotective responses to *Streptococcus pneumoniae* and tetanus. Based on these findings, immunoglobulin replacement was initiated with intravenous immunoglobulin (IVIG) at 0.5 g/kg/month, which is standard dosing.

Despite adequate weight-based dosing, the serum IgG failed to rise, remaining in the 200 mg/dL range after

more than three monthly IVIG infusions at standard dosing (0.5 g/kg/month). Therapy was switched to subcutaneous immunoglobulin (SCIG), but after three months of SCIG at standard dosing (0.5 g/kg/month), the trough IgG remained persistently in the same low range. The trough IgG is the lowest level of IgG drawn before the next dose is due. This failure of appropriately dosed replacement therapy to raise serum IgG prompted a search for an alternative explanation for the profound hypogammaglobulinemia. The typical response to adequate replacement immunoglobulin dosing is expected to increase the IgG level to >300 mg/dL above the baseline IgG level. This did not occur in our patient.

Stool alpha-1-antitrypsin was ordered and was elevated at >1.13 mg/g (reference range: 0-0.50 mg/g), consistent with enteric protein loss. Serum albumin was 3.3 g/dL (reference range: 3.9-5.0 g/dL). Absolute lymphocyte count was normal at $1.54\times10^3$/uL (reference range: $1.30\text{-}3.40\times10^3$/uL). Urinalysis was normal and did not show protein loss. Urgent gastroenterology consultation was obtained, and the patient was subsequently diagnosed with celiac disease, leading to PLE. Tissue transglutaminase IgA was 33 CU (reference range: <22 CU). Transglutaminase IgG was normal (but also in the setting of hypogammaglobulinemia). High-risk antigen HLA-DQ2.5 (human leukocyte antigen DQ2.5) was present. Mild villi atrophy was found on pathology results from upper endoscopy, but this was done while he was already on a mostly gluten-free diet for three months (in June 2023). The biopsy also showed preserved lamina propria plasma cells which pointed away from the diagnosis of CVID enteropathy. Based on the gathered information, and despite only mildly positive tissue transglutaminase and mild villi atrophy, the diagnosis of celiac disease was made as a diagnosis of exclusion. CVID enteropathy was considered, but ultimately the likelihood of celiac disease was greater.

Notably, the patient had no gastrointestinal symptoms, reported no symptoms associated with gluten ingestion, and consumed gluten regularly in his diet. After one year on a gluten-free diet and remaining on replacement immunoglobulin, his IgG started to increase, and eventually, he was able to discontinue the use of replacement immunoglobulin. Fecal alpha-1-antitrypsin test has returned normal. Serum albumin is 4.6 g/dL. Celiac antibody testing is normal as well. Most recent IgG levels were 905 mg/dL off replacement immunoglobulin for at least six months. He continues to do well and remains asymptomatic. He is without any prolonged, lingering infections, has improved fatigue levels, and is on a strict gluten-free diet.

Figure *1* demonstrates the patient's IgG over time. IVIG was initiated in December 2021, and the trough IgG levels remained low. Gluten-free diet was started in March 2023, but he was strictly adherent to the diet around March 2024. IVIG was discontinued in June 2025. Table *1* demonstrates his baseline test results in tabular form.

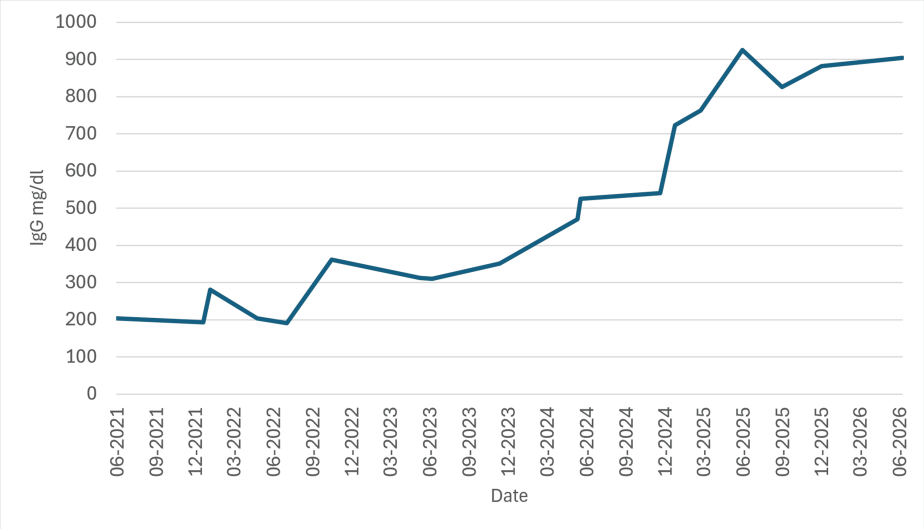



**FIGURE 1: IgG serum over time**

IgG: immunoglobulin G

| Test ordered | Result | Reference range | Date |
|---|---|---|---|
| IgG | 204 mg/dL | 726-1521 mg/dL | June 2021 |
| IgA | 54 mg/dL | 87-426 mg/dL | June 2021 |
| IgM | 77 mg/dL | 40-250 mg/dL | June 2021 |
| *Streptococcus pneumoniae* IgG | 5 out of 23 protective | Greater than or equal to 16 out of 23 | June 2021 |
| Serum albumin | 3.3 g/dL | 3.9-5.0 g/dL | June 2021 |
| Absolute lymphocyte count | $1.54\times10^3$/uL | $1.30\text{-}3.40\times10^3$/uL | June 2021 |
| Aspartate aminotransferase | 46 U/L | 13-62 U/L | June 2021 |
| Alanine aminotransferase | 47 U/L | 8-70 U/L | June 2021 |
| Tetanus IgG | 0.8 IU/mL | >0.1 IU/mL | June 2021 |
| Urine protein | Negative | Negative | June 2021 |
| Stool alpha-1-antitrypsin | >1.13 mg/g | 0-0.50 mg/g | December 2022 |
| Transglutaminase IgG | <20 CU | <20 CU | December 2022 |
| Tissue transglutaminase IgA | 33 CU | <22 CU | December 2022 |
| HLA-DQ2.5 | Present | Absent | December 2022 |

**TABLE 1: Baseline results: pre-diagnosis and treatment**

CU: chemiluminescent units; mg/dL: milligrams per deciliter; mg/g: milligrams per gram; IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; HLA: human leukocyte antigen; g/dL: grams per deciliter; $\times10^3$/uL: $\times10^3$ per microliter; U/L: units per liter

## Discussion

This case illustrates three clinically important points. First, PLE causes nonselective loss of plasma proteins, so hypogammaglobulinemia can be a manifestation of enteric protein loss rather than of a primary antibody deficiency [2]. Second, when serum IgG fails to rise despite adequately dosed IVIG and SCIG, ongoing loss of immunoglobulin should be suspected and enteric protein loss quantified. Third, celiac disease can cause clinically significant protein loss and hypogammaglobulinemia even in the complete absence of gastrointestinal symptoms [3].

The failure of immunoglobulin replacement to raise serum IgG is the pivotal diagnostic clue in this case. Adequately dosed IVIG (500 mg/kg/month) and a subsequent trial of SCIG left the serum IgG essentially unchanged in the 200 mg/dL range. In the setting of an intact replacement regimen, persistently low IgG points to accelerated clearance or ongoing loss rather than to inadequate supplementation. Enteric protein loss is quantified by measuring fecal alpha-1-antitrypsin, an endogenous serum glycoprotein of a size similar to albumin that is neither actively secreted nor absorbed and resists luminal proteolysis distal to the stomach, making it a reliable marker of gastrointestinal protein loss [2,6,7]. In this patient, the elevated stool alpha-1-antitrypsin redirected the workup from primary immunodeficiency toward a gastrointestinal source of protein loss.

Celiac disease is a well-recognized cause of PLE, and the magnitude of protein loss correlates with the degree of villous atrophy and improves with a gluten-free diet [2]. Celiac disease can present at any age with highly variable manifestations, ranging from classic malabsorptive symptoms to entirely asymptomatic disease, and chronic complications may include hypoalbuminemia and other consequences of malabsorption [8]. Importantly, celiac disease has been reported to cause profound and reversible hypogammaglobulinemia that corrects with a strict gluten-free diet, and the authors of that report emphasized a low threshold for celiac serology in patients with hypogammaglobulinemia even when gut symptoms are minimal or absent [4]. The present case reinforces that recommendation in a patient who consumed gluten regularly yet reported no gastrointestinal symptoms whatsoever.

The coexisting low IgA in this patient merits attention. Selective IgA deficiency occurs in 2-4% of patients with celiac disease and can produce false-negative results on IgA-based tissue transglutaminase (tTG-IgA) screening, so measurement of total serum IgA is essential during celiac evaluation; when IgA is deficient, IgG-based assays such as IgG anti-deamidated gliadin peptide or IgG tTG should be used [9,3]. Conversely,

routine serologic screening for celiac disease may itself uncover IgA deficiency and, on further testing, broader pan-hypogammaglobulinemia [5]. The relationship between IgA deficiency and celiac disease is complex and bidirectional, with IgA deficiency sometimes evolving after celiac diagnosis and the initiation of a gluten-free diet [10]. Our patient's IgG tTG was normal, but this was in the setting of very low serum IgG, thus suggesting a possible false-negative result. His serum IgA was low, but he still had an elevated tTG-IgA, which suggested possible celiac disease diagnosis.

The patient had a diet that was mostly gluten-free when the endoscopy was done which showed mild villous atrophy. Possibilities of this include slow or incomplete mucosal healing or ongoing gluten exposure [3]. Another cause of villous atrophy, CVID enteropathy, was considered unlikely for three reasons: our patient had intact pneumococcal and tetanus vaccine responses, no significant history of infections, and preserved plasma cells in the lamina propria. Absence of lamina propria plasma cells is the most characteristic histologic feature of CVID enteropathy [11].

Before attributing refractory hypogammaglobulinemia to a primary immunodeficiency such as CVID, secondary and reversible causes should be systematically excluded [1]. The diagnostic approach to suspected PLE involves excluding hepatic, renal, and nutritional causes of hypoproteinemia, documenting enteric protein loss with fecal alpha-1-antitrypsin, and pursuing targeted endoscopic, histologic, and imaging evaluation to identify the underlying cause [2,12]. Early identification of a treatable secondary cause, here, celiac disease, allows for cause-specific therapy rather than indefinite, and in this case ineffective, immunoglobulin replacement.

Distinguishing celiac-associated PLE from CVID enteropathy was particularly relevant in our patient. Celiac-associated PLE parallels the severity of villous injury and resolves with a gluten-free diet [2]. Because enteric protein loss is nonselective, albumin and immunoglobulins decline together. In CVID, by contrast, IgG, IgA, and IgM are disproportionately reduced, specific vaccine responses are impaired, and switched memory B cells are decreased [13]. CVID enteropathy usually needs corticosteroid therapy for treatment [11]. Our patient improved on a gluten-free diet alone, without corticosteroids, which supports celiac disease as the cause of his PLE.

## Conclusions

Celiac disease should be considered in the differential diagnosis of secondary hypogammaglobulinemia, including in patients without gastrointestinal symptoms and in those who report adherence to a gluten-free diet. Persistently low serum IgG despite adequately dosed immunoglobulin replacement should prompt evaluation for enteric protein loss, such as stool alpha-1-antitrypsin clearance. Recognizing celiac disease-associated PLE is important because it is a reversible cause of hypogammaglobulinemia that can mimic primary immunodeficiency, and treating it with a gluten-free diet may avoid misdiagnosis of CVID and unnecessary long-term immunoglobulin replacement.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Ami Thakor Philipp, Surina Kajani

**Acquisition, analysis, or interpretation of data:** Ami Thakor Philipp, Lorraine Anderson

**Drafting of the manuscript:** Ami Thakor Philipp, Surina Kajani

**Critical review of the manuscript for important intellectual content:** Ami Thakor Philipp, Lorraine Anderson

**Supervision:** Ami Thakor Philipp

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