Celiac Disease and Secondary Amyloidosis: A Possible Causal Association?

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ABSTRACT
We report a rare case of secondary renal amyloidosis in a patient with probable celiac disease presenting as nephrotic syndrome. A 30-year-old man with chronic diarrhea presented with progressive anasarca for 2 years. On further evaluation, he had hypoalbuminemia, significant nephrotic-range proteinuria, and elevated levels of anti-tissue transglutaminase. Renal biopsy suggested deposition of amorphous Congo red-positive material in the glomerular mesangium, positive for amyloid A amyloidosis. Endoscopic duodenal biopsy suggested blunting of the villous architecture and chronic inflammation of the lamina propria. The patient subsequently developed massive pulmonary embolism and died due to refractory cardiogenic shock.

INTRODUCTION
Celiac disease is a common enteropathy caused by a gluten-mediated inflammatory response among genetically predisposed individuals. The diagnosis is based on a combination of serology and small bowel biopsy. The value of serum anti-tissue transglutaminase (TTG) antibody has been extensively studied, and its specificity for celiac disease is 96–100%.1 Dietary avoidance of gluten results in the resolution of signs and symptoms.2 Celiac disease has a variety of extraintestinal manifestations including cardiac, hepatic, rheumatologic, endocrine, and neurologic involvement.3-12

CASE REPORT
A 30-year-old man presented with bilateral symmetric lower-limb edema, which progressed over 1 year to involve the rest of his body. He reported no fever, hematuria, joint pain, or skin changes. He experienced intermittent loose stools for 15 years, which lasted 3–5 days and were self-limiting, occurring once every 3–6 months. Stools did not contain mucus or blood, and he did not seek medical attention for this symptom. He had no history of hypertension, diabetes mellitus, or any malignancy. He was a vegetarian and did not smoke or consume alcohol.

His temperature was 36.5°C, and other vitals were blood pressure 100/70 mm Hg, heart rate 92 beats/min, and basal metabolic index 22.04 kg/m². Abdominal exam was notable for shifting dullness indicating ascites, while the cardiorespiratory and neurologic examinations were normal. Laboratory findings revealed microcytic hypochromic anemia (hemoglobin 10.1 g/dL, with transferrin saturation of 7%). White blood cells, platelets, erythrocyte sediment rate, serum creatinine, and serum urea were all normal. He had nephrotic-range proteinuria (4.3 g/d), marked hypoalbuminemia (<0.01 g/dL), and elevated serum cholesterol (230 mg/dL).
The workup for nephrotic syndrome included serology for blood-borne viral infections, all of which were negative. Renal biopsy suggested enlarged glomeruli with large mesangial matrix (Figure 1). The deposition of a pink hyaline eosinophilic substance was noted in the mesangium and peripheral capillary walls on staining with Congo red stain, which showed apple-green birefringence under polarized light. The immunofluorescence study showed globally sclerosed glomeruli and granular deposits of C3, C1q, κ, and λ as cotton wool deposits in the mesangium and walls of afferent arterioles. The deposits were positive for amyloid. These findings were suggestive of secondary amyloidosis involving the glomeruli, interstitium, and blood vessels.

Stool culture revealed no pathogenic organism. The patient had an elevated serum anti-TTG antibody of 28.4 SμL/dL. Subsequent esophagogastroduodenoscopy showed loss of duodenal fold on gross visualization, and biopsy revealed focal villous atrophy with numerous intraepithelial lymphocytes and chronic inflammatory cells in the lamina propria (Figure 2). In the light of these findings, the patient was started on a gluten-free diet for celiac disease, thought to be a possible etiology for amyloid A (AA) amyloidosis.

He presented 1 week later with ongoing anasarca and hypotension. Computed tomography of the chest and abdomen revealed a thrombus in the left main pulmonary artery. The lung fields and the mediastinal and abdominal structures were normal, and the vasculature showed no evidence of thrombosis. The patient developed massive hemoptysis, which prevented intravenous thrombolysis, and he died due to refractory cardiogenic shock.
DISCUSSION

Amyloidosis is characterized by the extracellular deposition of insoluble \( \beta \)-pleated chain protein fibrils.\(^{13} \) Amyloid protein is a derivative of serum amyloid A protein (SAA), the apolipoproteins associated with high-density lipoprotein in plasma, which is transcriptionally regulated by inflammatory cytokines.\(^{14} \) SAA protein levels have also been correlated with disease activity and progression, including renal dysfunction.\(^{15} \) Patients with higher SAA levels have a higher burden of AA deposition, which is estimated by whole-body serum amyloid P component scintigraphy.\(^{16} \) Patients with nephrotic syndrome have been found to have amyloid deposits predominantly in the glomerulus. Those with tubulointerstitial deposition developed progressive renal failure and defects in renal concentration capacity.

Our patient developed nephrotic syndrome secondary to glomerular AA deposits. The underlying etiologies of secondary amyloidosis include chronic inflammatory arthritis, periodic fever syndromes, inflammatory bowel disease, neoplasms, and infections.\(^{16-18} \) Autoimmune disorders were ruled out by negative serology; he was evaluated for liver disease and underwent CT chest and abdomen imaging to rule out possible infective foci or malignancies. The serological evidence of celiac disease, i.e., serum anti-TTG positivity in our case, favored the likelihood of celiac disease in the presence of villous atrophy and inflammatory changes in duodenal biopsy. We couldn’t measure the SAA levels, and the workup was limited by the lack of human leukocyte antigen typing, bone marrow, and salivary gland biopsy.

The T cell-driven inflammation triggered by gluten ingestion results in the release of pro-inflammatory cytokines in celiac disease. These cytokines can elevate SAA, although original studies testing this hypothesis are lacking. Isolated cases of cutaneous amyloidosis, both primary and secondary, have been reported to be associated with celiac disease.\(^{18,19} \) However, there is only one other case reported in the literature about the association between celiac and systemic secondary amyloidosis.\(^{20} \) To our knowledge, our case is only the second reported of its kind, and it underscores the importance of considering celiac disease as a possible etiology of secondary renal amyloidosis.

DISCLOSURES

Author contributions: A. Chhoda and D. Jain wrote the manuscript. MK Daga edited the manuscript. V. Batra interpreted the pathology slides. A. Chhoda is the article guarantor.

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Informed consent was obtained from the patient’s next of kin for this case report.

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Figure 2. Hematoxylin and eosin stains of the duodenal biopsy. (A) Low-power view showing fusion and flattening of villous folds \((\times 100)\). (B) High-power view showing focal increase in intraepithelial lymphocytes and increased chronic inflammatory cell infiltrate in the lamina propria \((\times 200)\).

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