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Subclinical Celiac Disease and Crystal-Induced Kidney Disease Following Kidney Transplant

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Abstract

Decreased kidney function from kidney deposition of calcium oxalate has been previously described in inflammatory bowel disease as well as following jejuno-ileal and Roux-en-Y gastric bypass surgeries. Although celiac disease is the most prevalent bowel abnormality associated with intestinal malabsorption, its relationship to high kidney oxalate burden and decreased kidney function has not been established. We report a case of subclinical celiac disease and hyperoxaluria that presented with loss of kidney function as a result of high oxalate load in the absence of overt diarrhea, documented intestinal fat malabsorption, and nephrolithiasis. Subclinical celiac disease is commonly overlooked and hyperoxaluria is not usually investigated in kidney patients. We propose that this entity should be suspected in patients with chronic kidney disease in which the etiology of kidney damage has not been clearly established.

Keywords

Hyperoxaluria; calcium-oxalate crystals; celiac sprue; celiac disease

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Introduction

Enteric hyperoxaluria, a condition described in inflammatory bowel disease and after bowel resection, is associated with an increased risk of kidney stones¹. Previous studies have shown jejuno-ileal and Roux-en-Y gastric bypass surgeries, used for the treatment of morbid obesity, are associated with enteric hyperoxaluria, calcium oxalate nephrolithiasis, and oxalate-induced kidney disease²⁻⁵. Celiac disease is the most prevalent enteric disease associated with intestinal malabsorption,⁶ and it has been shown that the degree of hyperoxaluria in celiac disease is associated with fat malabsorption⁷. In patients with untreated celiac disease, hyperoxaluria from intestinal oxalate overabsorption increases the risk of nephrolithiasis^{8,9}. However, the association between subclinical celiac disease and oxalate crystal-induced kidney damage has not been established. This teaching case describes the association between untreated subclinical celiac disease and kidney damage due to high oxalate burden in absence of nephrolithiasis and overt fat malabsorption.

Case Report

Clinical History and Initial Laboratory Data

A 57-year-old healthy Caucasian female presented for a routine examination. Past history was unremarkable except for mild hypertension and occasional diarrhea. Incidental abnormal laboratory data showed serum creatinine of 2.0 mg/dL (177 μ mol/L), corresponding to an eGFR of 26 mL/min/1.73 m² (0.43 mL/s/1.73 m²; calculated using the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation)¹⁰, and mild anemia with a hemoglobin of 9.0 g/dL (90 g/L) and hematocrit of 30.7%. Mean corpuscular volume was 89 femtoliter and mean corpuscular hemoglobin was 33 gm/dl (330 g/L). Upper and lower GI endoscopies disclosed no abnormalities to account for anemia. There were no overt explanations for reduced eGFR. On follow-up examination two years later, she was found to have further deterioration of kidney function with serum creatinine of 5.3 mg/dL (469 μ mol/L; eGFR, 9 mL/min/1.73 m² [0.15 mL/s/1.73 m²]) despite well-controlled hypertension.

Kidney Biopsy

A native kidney biopsy showed evidence of focal segmental glomerulosclerosis, global sclerosis, and incidental calcium oxalate crystal deposits (Figure 1A). Careful history excluded gastrointestinal symptoms, over ingestion of ascorbic acid or other oxalate precursors, and family history suggestive of primary hyperoxaluria. Decreased kidney function was therefore attributed to hypertension. However, over the following months, kidney function further deteriorated despite well-controlled hypertension and dialysis was initiated. After 3 months, she received a living-related donor kidney transplant.

The initial post-transplant course was uneventful with nadir serum creatinine of 1.1 mg/dL (97 μ mol/L; eGFR, 51 mL/min/1.73 m² [0.85 mL/s/1.73 m²]). However, over 8 weeks, kidney function progressively declined with serum creatinine ranging between 1.8 – 2.8 mg/dL (159 – 248 μ mol/L)(Figure 2), corresponding to eGFR of 29 - 17 mL/min/1.73 m² (0.48–0.28 mL/s/1.73 m²), resulting in three successive kidney allograft biopsies. The first

biopsy, performed three weeks following transplant when the serum creatinine was 6.0 mg/dL (530 μ mol/L; eGFR 7 mL/min/1.73 m² [0.12 mL/s/1.73 m²]), showed occasional calcium oxalate crystal deposits which were irregular, laminated or fan shaped, and colorless under ordinary light but clearly birefringent under polarized light (Figure 1B). The glomeruli and tubules were intact and there was no evidence of cellular infiltrate to suggest allograft rejection. The second percutaneous biopsy performed eight weeks post-transplant showed many more calcium oxalate crystals with associated tubular injury as well as areas of patchy interstitial lymphocytic infiltrate (Figure 1C). These findings were considered consistent with mild cellular rejection and/or oxalate kidney disease. Despite anti-rejection treatment, serum creatinine further deteriorated. At fourteen weeks post-transplant, a third biopsy showed evidence of extensive calcium oxalate deposition (Figure 1D). Two 24-hour urine collections during this period showed urinary oxalate excretion ranging between 97–130 mg/day (1077–1443 μ mol/day) (normal <40 mg/day (444 μ mol/day)). At this time, oxalate kidney disease was suspected.

Diagnosis

A metabolic evaluation was performed on a restricted metabolic diet both prior to and following dietary gluten restrictions (Table 1). Normal urinary glycolate and L-glycerate ranging between 19.7–33 ug/mg Cr (normal <70 ug/mg Cr) and 0–0.1 ug/mg Cr (normal <19 ug/mg Cr), respectively, excluded primary hyperoxaluria biochemically. Moreover, unclassified primary hyperoxaluria was excluded since plasma glycolate was normal at 26 μ M (normal = 21–193 μ M). Quantitative stool fat content during a 72-hour collection was 1.3 g (normal <7 g), thus excluding fat malabsorption. However, stool quantity was markedly elevated at 1369 g (normal <500 g). Serological tests showed mildly elevated anti-gliadin IgG antibody at 28.5 EU (normal <25 EU), normal anti-gliadin IgA antibody at 8.2 EU (normal <25 EU), and uncertain anti-tissue transglutaminase antibodies (anti-tTGA) at 7 U/ml (equivocal range 5–8 U/ml). Due to the borderline level of serum anti-gliadin IgG, a small intestine biopsy was performed demonstrated normal mucosal architecture without the classical flattening of gluten-induced celiac disease (Figure 3A).

Clinical Follow-up

The patient was started on dietary gluten restrictions with a fall in urinary oxalate from 128 mg/day (1421 μ mol/day) to a normal level throughout the follow-up, with the exception of a short period (Table 1, Figure 2). Total urine volume, pH, sodium, potassium, phosphorus, calcium, magnesium, and citrate increased with dietary gluten restrictions (Table 1). Commensurate with the fall in urinary oxalate, serum creatinine declined from 1.7 mg/dl (150 μ mol/L) to 1.2 mg/dl (106 μ mol/L), corresponding to an increase in eGFR from 31 to 46 mL/min/1.73 m² [0.52 to 0.77 mL/s/1.73 m²]). Based on the above findings, the diagnosis of kidney allograft failure due to calcium oxalate crystal deposition as a result of celiac disease was reached.

Discussion

This is an instructive case describing the relationship between subclinical celiac disease and oxalate-induced kidney disease in both native and allograft kidneys. Previous studies have

also shown overt enteric hyperoxaluria in association with increased tissue oxalate burden and consequent GFR loss^{11–13}.

Celiac disease can present as a subclinical rather than overt disorder with its late diagnosis leading to significant morbidity and mortality^{14–17}. In our patient, the typical clinical manifestations of celiac disease were masked and an early diagnosis was missed. This case highlights the notion that subclinical celiac disease and its accompanying hyperoxaluria should be carefully explored as etiologic causes of unexplained kidney allograft failure.

The gold standard for the diagnosis of celiac disease is abnormal intestinal mucosal architecture. However, it has been proposed that the small bowel mucosal lesion of celiac disease is heterogeneous, ranging from normal mucosa and increased intraepithelial lymphocytes to the classical finding of flat mucosal lining¹⁸. The normal intestinal biopsy in this case (Figure 3A) may reflect this heterogeneous distribution and sampling error. Single intestinal biopsy specimen may not be sufficient to establish the diagnosis since stringent diagnostic criteria require multiple biopsies¹⁹. Another possible complication is that abnormal mucosa may normalize shortly after a decrease (perhaps unintended) in gluten intake. Although subsequent intestinal biopsies were not indicated nor performed after the patient started dietary gluten restrictions, in this case a concomitant fall in serum creatinine and urinary oxalate strongly suggests dietary gluten restrictions resolved the hyperoxaluria and kidney disease (Figure 2). Four months following dietary gluten restrictions, total fecal weight decreased from 1369 g to 539 g, and total fecal lipid content did not change significantly.

One curious finding is that high stool volume was not associated with increased fecal fat content. A widely perceived mechanism for increased urinary oxalate excretion is enhanced binding of luminal fat with divalent cations facilitating intestinal oxalate absorption^{7,12}. The finding of increased stool volume suggests an impaired salt and water transport defect throughout the intestine from either defective absorption and/or secretion. Hyperoxaluria could conceivably have occurred due to the altered permeability of the intestinal epithelia to oxalate, resulting in absorption. Both paracellular and transcellular pathways are believed to contribute to oxalate movement in the gut, yet the relative significance of these pathways has not been fully elucidated. A recent study has speculated that net dietary oxalate absorption is governed by the relative balance between absorption and transcellular secretion governed by the oxalate transporter SLC26A6²⁰. In rodents, SLC26A6 has been previously described to mediate intestinal oxalate secretion, and gene deletion results in inhibition of intestinal oxalate secretion, hyperoxalemia, and secondary “spill-over” hyperoxaluria^{21–23}. One could hypothesize that damaged epithelium in our patient with celiac disease may result in lower protein expression of SLC26A6, favoring intestinal oxalate absorption. It is also plausible that subclinical celiac disease with an inflammatory response may have stimulated intestinal oxalate absorption through a cytokine-mediated paracellular “leak pathway”²⁰. Therefore we used immunofluorescence staining to examine the protein expression of SLC26A6 in the small bowel of our case and an unaffected control (Figure 3). In the control, SLC26A6 signal was evident on the surface of the microvilli as well intracellularly (bottom row). While villin staining was preserved, SLC26A6 staining appeared to be much reduced in our subject (top row). We are cognizant that immunohistochemistry is not quantitative,

but in our view the difference in staining is quite remarkable. This raises the possibility that reduction of intestinal oxalate secretion may also be a mechanism of hyperoxaluria in humans. This finding will need to be further examined in patients with intestinal hyperoxaluria.

In our case, the possibility of increased tissue oxalate burden caused by diminished kidney excretion is remote. Although serum oxalate concentrations increase in patients with end stage kidney disease ^{24,25}, this rise is not associated with significant tissue accumulation of oxalate since the rise in urinary oxalate following transplant is transient ^{25–27}. This situation is unlike that of our case where hyperoxaluria and crystal-induced decrease in kidney function occurred several weeks after transplant. Calcium oxalate deposition was reported in 4% of unselected kidney biopsy specimens from one study ^{13,28}. Interstitial calcium oxalate deposit is not a prominent feature in patients with calcium oxalate stones ⁴⁵. A higher incidence is shown in allograft biopsy and allograft nephrectomy specimens ^{28–30}.

Unlike oxalate kidney disease complicating Roux-en-Y gastric bypass ⁵, kidney function in our patient improved and was sustained within a normal range during the 52-month follow-up. One major difference between this case and oxalate burden detected in jejuno-ileal or Roux-en-Y gastric bypass is that adherence to a dietary gluten restrictions leads to a full recovery of kidney function.

In conclusion, the diagnosis of calcium oxalate-induced kidney failure from enteric hyperoxaluria due to subclinical celiac disease may be cumbersome and difficult because intestinal biopsies, a gold standard for the diagnosis of celiac disease, is invasive and sampling may be heterogeneous. However, practicing nephrologists must be aware of the fact that hyperoxaluria and resultant kidney oxalate deposition is a reversible cause of kidney failure, and that intestinal hyperoxaluria can exist with minimal or no intestinal symptoms. The addition of urinary oxalate measurements and careful serological investigations should be considered to explore this possibility in patients with unexplained kidney failure.

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Figure 1.

Native and allograft kidney biopsy. A) Light microscopy of native kidney biopsy showed a total of 17 glomeruli with 6 globally sclerotic. Left panel: No hypercellularity or crescent formation was seen. There was tubular atrophy and dropout with interstitial fibrosis, and crystals were present in the tubules. Right panel: Under polarized light, the crystals were birefringent consistent with calcium oxalate crystals. B) Allograft biopsy 3 weeks post kidney transplant: Tubule showing occasional refractile acellular deposits and birefringent crystals under a polarized lens. C) Allograft biopsy 8 weeks post kidney transplantation:

calcium oxalate crystals seen within tubular lumen and within tubular epithelial cells with associated tubular injury. Birefringent calcium oxalate crystals seen in many tubular lumens and tubular epithelial cells. D) Allograft biopsy 14 weeks post kidney transplant: Large refractile acellular deposits in several tubular lumens with associated tubular injury. Extensive birefringent calcium oxalate crystals within tubular lumina and within tubular epithelial cells. Left panels: hematoxylin and eosin stain (original magnification, $\times 200$); right panels: polarized lens (original magnification, $\times 100$). Courtesy of Dr James Wellons.

Figure 2. Clinical course of serum creatinine concentration and urinary oxalate excretion rate in relationship to the major clinical events. A) Kidney transplant. B) Oxalate crystals on post-kidney transplant biopsies (first biopsy, 3 weeks posttransplant; second, 8 weeks; third, 14 weeks). C) Oxalate restriction. D) Gluten-free diet started. E) Nonadherence to diet. F) Resumption of gluten-free diet.

Figure 3.

Architecture and SLC26A6 expression in the small intestine in biopsies from the patient (top row) and an unaffected control (bottom row). Left panels: intestinal biopsy showing normal mucosal architecture in patient and control (Hematoxylin and eosin stain; original magnification, $\times 100$). Middle and right panels: each cluster of 4 images shows (clockwise from top left) villin staining (green), DIC image, merged image, and SLC26A6 staining (red); original magnification, $\times 100$.

Table 1

Post-kidney transplant inpatient metabolic evaluation

24-h urine parameters	Baseline	4 mo after gluten restriction	p
Total Volume (L/d)	2.8 ± 0.9	3.5 ± 0.4	0.4
pH	5.58 ± 0.02	6.4 ± 0.36	0.06
Sodium (mEq/d)	41 ± 22	98 ± 18	0.01
Potassium (mEq/d)	16.7 ± 4.6	97.7 ± 1.1	<0.001
Phosphorus (mg/d)	370 ± 148	583 ± 10	0.1
Calcium (mg/d)	66.7 ± 46.3	109 ± 18	0.1
Magnesium (mg/d)	26 ± 18	57 ± 4	0.06
Citrate (mg/d)	20 ± 0	546 ± 14	<0.001
Oxalate (mg/d)	128 ± 21	68 ± 6	0.04
Glycolate (ug/mg Cr)*	33	19.7 ± 8.9	---
L-glycerate (ug/mg Cr)†	0	0.91 ± 0.36	---

Note: Values are expressed as mean ± standard deviation. Results represent the mean of two or three 24-hour urine collections with the exception of baseline glycolate and L-glycerate levels. Laboratory data were collected during a 4-day constant metabolic diet containing 400 mg calcium, 100 mEq sodium, 100 mg oxalate, and 800 mg phosphorus daily. Conversion factors for units: phosphorus in mg/day to mmol/day, ×0.03229; calcium in mg/day to mmol/day, ×0.02495; magnesium in mg/day to mmol/day, ×0.041; citrate in mg/day to mmol/day, ×0.00521; oxalate in mg/day to μmol/day, ×11.11.

* Normal <70 ug/mg Cr

† Normal <19 ug/mg Cr