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Kidney Biopsy Teaching Case

Oxalate Nephropathy and Intravenous Vitamin C

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Oxalate nephropathy is a rare condition characterized by extensive calcium oxalate deposition in the renal tubules, resulting in kidney injury. There are primary forms of the disease that arise from genetic mutation causing overproduction of oxalate. More commonly, this condition is seen as a secondary phenomenon. The clinical presentation is nonspecific, with acute kidney injury and normal serologic study results. The characteristic finding on kidney biopsy is the presence of acute tubular injury associated with polarizable crystals in the tubular lumen and epithelial cytoplasm. We present a case of acute oxalate nephropathy in a patient with underlying systemic lupus erythematosus who recently received intravenous vitamin C.
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INDEX WORDS: Oxalate; oxalosis; acute kidney injury; acute renal failure; alternative medicine; traditional medicine; vitamin C; ascorbic acid; lupus; systemic lupus erythematosus (SLE).

INTRODUCTION

Oxalate nephropathy occurs when calcium oxalate crystallizes within the renal tubules and epithelium. The resulting crystals induce damage to the tubular epithelium, leading to acute tubular injury and a clinical presentation of acute kidney injury.[1] Traditionally, hyperoxaluria is divided into hereditary and acquired forms. Hereditary hyperoxaluria is subdivided into 3 types: primary hyperoxaluria (PH)1, PH2, and PH3. PH1 is the most common and is caused by a deficiency of the liver-specific pyridoxal-phosphate–dependent enzyme alanine-glyoxylate aminotransferase (encoded by the *AGXT* gene). PH2 results from a deficiency in the cytosolic enzyme glyoxylate reductase/hydroxypyruvate reductase (encoded by *GRHPR*), whereas the recently described PH3 appears linked to *HOGA1* (formerly DHDPSL), a gene that encodes a mitochondrial enzyme.[2] Acquired forms result from exogenous ingestion of high-oxalate–containing substances, especially in the setting of chronic kidney disease.[3] Other causes of acquired hyperoxaluria are enteric hyperabsorption of normal dietary oxalate in the context of underlying gastrointestinal disease, iatrogenic methoxyflurane or parenteral xylitol administration, gastric bypass surgery, pyridoxine deficiency, and ethylene glycol ingestion.[3,4]

Oxalate is present in many foods and is ingested with impunity under normal circumstances (Box 1).[5-7] Serum oxalate levels increase rapidly in response to ingestion of high-oxalate–containing foods, and absorption is affected by multiple factors, including absorption capacity to intestinal transit time.[8,9] While less commonly encountered, intravenous (IV) injection of drugs containing either calcium oxalate or oxalate precursors also can produce oxalate nephropathy.

CASE REPORT

Clinical History and Initial Laboratory Data

A 51-year-old woman with a history of systemic lupus erythematosus, anemia of chronic disease, pleural and pericardial effusions, and arthralgias presented with refractory nausea and vomiting, lethargy, and weakness for the previous 7 days. The patient reported the use of ibuprofen and acetaminophen. At presentation, she had a serum creatinine level of 7.2 mg/dL (corresponding to an estimated glomerular filtration rate [eGFR] of 6 mL/min/1.73 m^2 calculated using the 4-variable Modification of Diet in Renal Disease [MDRD] Study equation) with a baseline creatinine level 8 months earlier of 0.9 mg/dL (eGFR, 66 mL/min/1.73 m^2).[10] Laboratory test results also were remarkable for a serum calcium level of 12.3 mg/dL. The patient's chronic anemia had worsened from a baseline hemoglobin level of 9.6 to 7.8 g/dL, with hematocrit of 23.2% and mean corpuscular volume of 85 fL.

The patient was admitted to the hospital and treated with aggressive IV hydration. By the following day, a small improvement in creatinine level was noted, although urine output remained minimal. Urine was turbid and yellow, with protein (1+), 77 white blood cells per high-power field, no hematuria, rare bacteria, and hyaline (21 per low-power field) and granular (4 per low-power field) casts. Serologic studies were positive for antinuclear antibodies with a homogenous pattern at a 1:1,280 titer. Antibodies to anti–double-stranded DNA, anti-RNP, anti-chromatin, and anti-Sjögrens A and B also were present. Hepatitis B and C panels were negative. On hospital day 2, treatment with methylprednisolone was started and kidney ultrasonography and biopsy were performed. The kidney ultrasound suggested medical kidney disease bilaterally.

Kidney Biopsy

Light microscopy sections showed 20 glomeruli, none globally sclerosed. Diffuse mild mesangial hypercellularity was present

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Box 1. Foods With High Oxalate Content

Grains
- All Bran (Kelloggs)
- Buckwheat flour
- Barley
- Cornmeal
- Wheat flour and bran
- Brown rice flour
- Spaghetti
- Tortilla

Seeds, legumes, and nuts
- Almonds
- Tahini
- Mixed nuts with or without peanuts
- Sesame seeds
- Cashew nuts
- Hazelnuts
- Peanut butter
- Peanuts
- Pecans
- Chili beans
- Black beans
- Navy beans

Fruit and vegetables
- Beets
- Miso
- Rhubarb
- Spinach
- Swiss chard
- Chocolate soy milk
- Star fruit
- Okra
- Collard greens
- Mustard greens
- Potatoes
- Sweet Potatoes
- Tomatoes (canned)
- Apricots
- Figs
- Kiwi fruit

Source: The Oxalosis and Hyperoxaluria Foundation.[7]

(Fig 1A). No endocapillary hypercellularity, fibrinoid necrosis, crescent formation, wire loops, or hyaline thrombi were noted. The interstitium showed diffuse edema with no significant inflammatory infiltrate. Minimal interstitial fibrosis and tubular atrophy were present. Tubular lumens were dilated, with epithelium showing reactive-appearing nuclei and diffuse epithelial simplification with loss of proximal tubule brush borders (Fig 1A). Tubular lumens contained numerous crystals consistent with calcium oxalate that were readily polarizable on hematoxylin and eosin–stained sections (calcium oxalate crystals dissolve during the periodic acid step of the periodic acid–Schiff stain; therefore, polarization should be attempted on hematoxylin and eosin–stained sections; Fig 1C and D). Rare calcium phosphate crystals also were present. There was extensive Tamm-Horsfall protein present in tubular lumens. Arteries and arterioles were unremarkable.

Sixteen glomeruli, one globally sclerotic, were present for evaluation by immunofluorescence microscopy. Sections were incubated with antibodies against immunoglobulin G (IgG), IgM, IgA, C3, C4, C1q, albumin, fibrinogen, and κ and λ light chains. There was predominantly mesangial staining by IgG (3+), IgM (2+), C3 (1+), C1q (trace), κ (3+), and λ (3+). There also was diffuse staining of the nuclei by IgG, commonly referred to as tissue antinuclear antibody pattern (Fig 1B). All other stains were negative. There was no significant extraglomerular staining.

Two glomeruli were present for ultrastructural evaluation and showed mesangial matrix expansion with scattered electron-dense deposits. Mild epithelial foot-process effacement was seen. No electron-dense deposits were present along the glomerular basement membrane. No tubuloreticular inclusions were identified.

Diagnosis

Acute oxalate nephropathy on top of mesangioproliferative lupus nephritis, International Society of Nephrology/Renal Pathology Society class II.

Clinical Follow-up

Additional clinical history showed the patient had recently received 2 IV doses of vitamin C at an alternative medicine clinic. She did not report recent ingestion of ethylene glycol or excessive intake of foods known to be rich in oxalic acid. There was no history of malabsorption or gastric bypass surgery. The patient was initiated on hemodialysis therapy, but by discharge was making ~400 mL of urine per day with a creatinine level of 5.4 mg/dL and eGFR of 8 mL/min/1.73 m^2. At her most recent follow-up, the patient had a stable creatinine level of 1.1 mg/dL and eGFR of 52 mL/min/1.73 m^2.

DISCUSSION

The etiology of hyperoxaluria from IV vitamin C most likely is related to endogenous conversion of ascorbic acid to oxalate.[11] In the setting of hyperoxaluria, calcium oxalate supersaturation can occur and form crystal nuclei. These early crystals usually form on epithelium, cellular debris, or urinary casts and are potentiated by increased uric acid, calcium, and oxalate or decreased citrate levels.[12,13] In healthy individuals, microcrystals are produced in the late segments of the nephron; however, these are quickly passed into urine without sufficient time to grow.[13,14] Intratubular retention of calcium oxalate crystals is believed to preferentially occur in areas of damaged and regenerating renal tubular epithelium, where many molecules with proposed crystal-binding capacity are expressed.[12]

The development of oxalate nephropathy in the setting of excessive administration of ascorbic acid was reported first in 1985 by Lawton et al.[15] We are aware of 5 additional reports of this disease in the world literature.[15-19] This suggests that it is a rare cause of acute kidney injury, although it may be underreported. Vitamin C injection is a treatment in alternative medicine that gained popularity after controversial articles showed treatment efficacy in patients with cancer.[11,20] It is used most commonly as treatment for fatigue, various cancers (breast cancer most commonly), and rickettsial and viral infections.[21] Recent survey data showed that responding practitioners administered vitamin C injections to more than 11,000 patients in 2006.[21] Alternative medicine practices are growing, with up to 80% of some populations receiv-