CASE REPORT

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Vitamin C-Induced Oxalate Nephropathy in a Septic Patient

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OBJECTIVES: Vitamin C is a novel treatment currently under investigation in the management of sepsis. Adverse renal effects of vitamin C through hyperoxaluria have been described in the past.

DATA SOURCES: We report the case of a 63-year-old man admitted in a community-based hospital with a diagnosis of sepsis of pulmonary origin.

DATA EXTRACTION: On day 19, despite a having developed oligoanuric acute kidney injury, a regimen of IV vitamin C, hydrocortisone, and thiamine was undertaken for 4 days. On day 23, the patient required renal replacement therapy with an estimated glomerular filtration rate of 7 mL/min. Renal biopsy revealed extensive acute tubular necrosis associated with the presence of intratubular crystal of calcium oxalate.

CONCLUSION: Although vitamin C seems to be a possible therapeutic asset in the supportive care of sepsis patients, larger cohorts are required to ensure its safety and underlying or novel kidney injury should forewarn clinicians as to its use.

KEY WORDS: acute kidney injury; ascorbic acid; nephropathy; renal replacement therapy; sepsis; vitamin C

Recent studies have suggested that the adjunctive treatment of vitamin C in septic choc reduces vasopressor need and might reduce mortality (1, 2). However, adverse renal effect of vitamin C through hyperoxaluria has been described in the past. We here describe the case of a patient with sepsis treated with high doses of vitamin C that developed biopsy-confirmed oxalate nephropathy.

A 63-year-old man of 70 kg was initially admitted to a community hospital with respiratory distress. His pertinent medical history was limited to chronic obstructive pulmonary disease (COPD). He was not known for any cardiac or renal diseases and had a normal renal function upon arrival with a glomerular filtration rate (GFR) of 92 mL/min/1.73 m^2 (creatinine 76 μmol/L). A community-acquired pneumonia with COPD exacerbation was diagnosed and IV moxifloxacin as well as corticosteroids were initiated upon admission. His respiratory state deteriorated shortly after admission and the patient was intubated to ensure adequate oxygenation.

The ICU stay was notable for difficult respiratory weaning and widening of the antibiotic spectrum. Moxifloxacin was ceased on day 9 of admission to the ICU, and IV ciprofloxacin was introduced from days 9 to 15 with the addition of piperacillin-tazobactam from days 9 to 19. Despite ongoing antibiotics, the patient became hypotensive and feverish on day 9. Hemocultures remained negative and cerebral, thoracic, and abdominal CT scans, as well as cardiac ultrasound, were unremarkable. A sepsis of unknown origin was diagnosed and antibiotic coverage was widened with the introduction of IV vancomycin on

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day 15. On day 19, piperacillin-tazobactam was substituted to meropenem, and fluconazole was introduced. Serum concentration of vancomycin was monitored with maximum concentration reaching 36.7 mg/L on day 19. Oligoanuric acute kidney injury (AKI) started to progress from day 15 with serum creatinine rising up to 409 μmol/L by day 18 despite aggressive fluid administration. On day 19, with a creatinine of 451 μmol/L, a regimen of 1,500 mg of IV vitamin C every 6 hours and IV hydrocortisone 100 mg every 6 hours as well as IV thiamine 200 mg IV every 12 hours was undertaken for a duration of 4 days. The patient was transferred to our facility on day 23 for renal replacement therapy (RRT) with a urea of 87.4 mmol/L, creatinine of 650 μmol/L with a estimated GFR of 7 mL/min.

Upon the patients' arrival in our hospital, urine analysis revealed microscopic hematuria and significant proteinuria (estimated 18 g/24 hr). Urine sediment revealed the presence of calcium oxalate crystals. Urinary sodium was measured at 95 mmol/L, urinary creatinine 5,754 μmol/L, serum sodium of Na 147 mmol/L, and serum creatinine of 650 μmol/L. The serum vitamin C was measured at 1,026 μmol/L (normal value 30–114 μmol/L). Anti-glomerular basement membrane antibodies, perinuclear anti-neutrophil cytoplasmic antibodies, and proteinase 3 anti-neutrophil cytoplasmic antibodies were negative. Antibiotics were withheld and continuous RRT was initiated. A renal biopsy revealed extensive acute tubular damage associated with the numerous intratubular translucent crystals. Under polarized light, these crystals showed birefringence, with irregular shapes, sometimes having a fan-like appearance, consistent with calcium oxalate crystals (**Fig. 1**). No interstitial fibrosis or tubular atrophy was noted. Glomeruli showed ischemic changes only, and arterial section revealed discrete intimal fibrosis. Immunofluorescence study did not show any significant staining. The patient required RRT for several weeks but eventually made a full renal recovery. After several months of physical rehabilitation, the patient was able to return home. Patient's written informed for publication of case details and images was obtained.

Vitamin C is an essential water-soluble vitamin. It is needed for collagen production, has a role in fatty acid transport, in the synthesis of multiple neurotransmitters and in the prostaglandins metabolism, and has antioxidant properties (3). Relative vitamin C depletion has been suggested to play a role in the pathogenesis

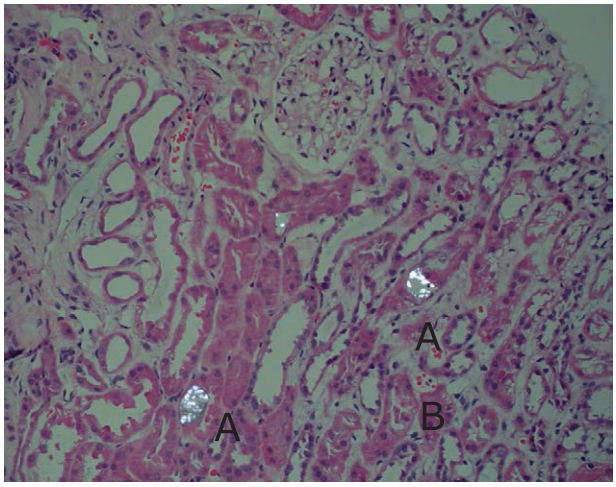

Figure 1. Renal biopsy performed in a 63-yr-old patient suffering from sepsis, acute kidney injury and having received high dose vitamin C. Under polarized light, intratubular birefringent oxalate crystal deposition can be seen (**A**) accompanied by interstitial mononuclear cell infiltration (**B**) and acute tubular injury (hematoxylin-eosin, original magnification ×200).

of sepsis (3). Proposed mechanisms of its action include attenuation of the pro-inflammatory response, enhancement of the endothelial and epithelial barrier function, and the prevention of sepsis-associated coagulation abnormalities (3).

There is currently uncertain clinical benefice for the use of vitamin C in sepsis. In 2016, Zabet et al (1) conducted a small randomized control trial on 28 patients. They compared the use of 25 mg/kg of IV vitamin C every 6 hours to placebo in septic patients. The results showed lower dose of vasopressors as well as reduced mortality in the vitamin C group. They did not see an increase in AKI in the treatment group. However, based on previous safety trials, bilateral ureteric obstruction, chronic hemodialysis, iron overload, and oxalate stone formers were excluded from the study (4). In 2017, Marik et al (2) published a before-after unicentric study comparing a cohort of septic patients receiving a fixed regimen of IV vitamin C (1.5 g every 6 hr), thiamine (200 mg every 6 hr), and hydrocortisone (50 mg every 6 hr) to placebo. The results showed striking lower mortality rate for patients treated with the combination of vitamin C, thiamine, and hydrocortisone without increase serious adverse events. Of note, 66% of the treated group and 64% of the control group were deemed to be in acute renal injury with traditional KDIGO definition at recruitment. Outcome concluded to a decrease in RRT (10% for treated group vs 33% of

control group). In spite of those studies, more recent randomized control trials have failed to demonstrate mortality benefits for septic patients with high-dose vitamin C (5, 6). Furthermore, a recent meta-analysis including 1,671 patients also failed to demonstrated mortality benefits of vitamin C in sepsis (7).

Regardless of potential mortality benefits, adverse renal effects of vitamin C have been well described. Indeed, ascorbic acids' metabolism leads to formation of oxalic acid. Furthermore, vitamin C augments oxalate intestinal absorption (8). Hyperoxaluria is in turn nephrotoxic as oxalate is directly toxic to epithelial cells of the renal tubule (8). Deposition of birefringent calcium oxalate crystals with or without associated lithiasis or nephrocalcinosis also contributes to acute tubular toxicity (8).

Over the years, case reports have been published highlighting this potential complication. Alkhunaizi and Chan (9) reported a case of a 58-year-old man of 70 kg, hospitalized for serious burn injuries. Along with parenteral nutrition, the patient received IV vitamin C at a dose of 1 g daily for 2 months. Subsequent oligoanuric acute kidney failure developed requiring RRT. A kidney biopsy showed signs suggestive of oxalate nephropathy with tubular injury and abundant oxalate crystal deposition. Other reports of secondary oxalosis attributed to parenteral nutrition have also been published (10, 11). In 2016, Buehner et al (12) reported two cases of young patients with previously normal kidney function who received high-dose IV vitamin C in the context of resuscitation post severe burn injuries. Having received 101 and 224 g of vitamin C over 18 and 20 hours, respectively, both patients developed severe oligoanuric AKI and died a few days after their hospital admission. Autopsy findings included oxalate nephropathy in both patients. More recently, Colliou et al (13) reported the case of a 57-year-old woman admitted in a critical care unit for septic shock who received IV vitamin C for 2 months and developed a biopsy-confirmed oxalate nephropathy. In 2020, two case reports, including three patients, have reported biopsy-proven oxalate nephropathy following high-dose IV vitamin C in the context of a coronavirus disease 2019 infection (14, 15). RRT was initiated in all three cases. Other cases of AKI with oxalate nephropathy after high dose of oral vitamin C have also been reported (16–19).

We here describe the case of a patient who received high-dose IV vitamin C as an adjunctive treatment of sepsis. The patient received a total of 85 mg/kg/d for four days of vitamin C. The patients' kidney biopsy revealed acute tubular injury with oxalate deposition following vitamin C therapy. The etiology of the AKI in this patient was surely multifactorial, with ischemic acute tubular necrosis and vancomycin toxicity contributing to the renal damage of the patient before the administration of vitamin C. However, the contribution of oxalate nephropathy must be taken into consideration. Because of potential of organ-threatening complications and inconsistencies found in current literature, further research will be require to conclude on the safety and efficacy of vitamin C in sepsis. Numerous ongoing randomized controlled trials will address the efficacy of vitamin C in sepsis and will hopefully help us shed a light its usage in the context of renal injury. Namely, the ongoing Lessening Organ Dysfunction With VITamin C (20) trial will exclude patients with previous kidney stones, and Ascorbic Acid, Corticosteroids and Thiamine in Sepsis trial (21) will exclude patients with a history of kidney stones and end-stage renal disease. The relevance of those studies is furthermore underlined by recent animal studies suggesting a potential role of megadose of vitamin C in the treatment of sepsis (22). Until further documentation, caution should be applied with the use of IV vitamin C in patients with acute renal injury and those with previous kidney stones.

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