Unexplained, Recurrent AKI in a Young Man—It Takes a Community

By Roger A. Rodby

A 28-year male from Asia, with no comorbidities; with no family history of kidney diseases; a non-smoker; an occasional alcohol drinker; with no use of nonsteroidal anti-inflammatory drugs/other drugs; and index presentation in October 2020 with nausea, generalized weakness, and on investigation creatinine was 2 mg/dL (no baseline creatinine). With hydration, acute kidney injury (AKI) self-resolved to creatinine 1.1 mg/dL in 1 month.

And so began a thread from a physician in India that was posted in the Open Forum of ASN Communities (1). Eight months later, it happened to the patient again: same symptoms, same AKI, and a similar resolution. An extensive history was taken and was negative for any ingestions, prodromes, fevers, etc. A urinalysis was normal, and a 24-hour urine collection showed 72 mg of proteinuria. Serologic testing included normal antinuclear antibody, cytoplasmic-antineutrophil cytoplasmic antibody (ANCA), and perinuclear-ANCA. Two months later, the patient had the same presentation and outcome. Six months after the initial presentation, he developed gross hematuria, and his creatinine peaked at 2.6 mg/dL. This time, the urinalysis had >100 red blood cell/high-powered field. An antistreptolysin O titer, C3, and C4 were in the normal range. He was then treated with intravenous pulse steroids, and within 1 week, his creatinine level was 1.2 mg/dL and urinalysis completely normalized. Two months following that AKI episode, he developed another AKI to 2.7 mg/dL but no hematuria this time, and a kidney biopsy was performed. It was read as normal kidney parenchyma. The kidney function resolved again within 1 week. For 1 year, he was symptom-free, and then he developed similar vague symptoms and gross hematuria: creatinine, 2.3 mg/dL. Within 1 week, it normalized to 1.1 mg/dL, and hematuria resolved. The patient exercised regularly with both resistance and aerobic training but was unable to associate any of these AKI events to his level of workout routine.

In 2016, ASN opened its online "ASN Communities": a physician blog that allows any ASN member to post a difficult case to which any other ASN member can contribute with comments, suggestions, or advice. This case of totally unexplained AKI is the kind of unusual case that we often see posted in the "Open" Communities forum.

The blog continued with questions from various ASN members of hemolysis, rhabdomyolysis, porphyria, and even paroxysmal nocturnal hemoglobinuria, even though the patient experienced hematuria not pigmenturia. Then, following several posts questioning the kidney biopsy, a contributing nephrologist, also from India, asked for a serum uric acid level. This was largely ignored until he posted his comment: "*A low serum uric acid may be a clue to the development of AKI with exercise or even otherwise due to a URAT1 [urate transporter 1] mutation*," at which point everyone jumped on the hypouricemic bandwagon! A uric acid was ordered and was extremely low at 0.3 mg/dL with a fractional excretion of uric acid of 120%. What then followed were several references to case reports of AKI associated with renal hypouricemia (RHUC) that were often preceded by exercise and sometimes associated with gross hematuria. The symptoms are relatively non-specific with malaise, often with flank pain, and typically with microscopic hematuria but can be gross. Microscopic examination of the urine may show uric acid crystals.

RHUC is a rare genetic condition in which there is impaired tubular transport of uric acid in the proximal tubule. As a result, the serum uric acid is very low (<2%) associated with a high fractional excretion of uric acid (>10%). Type 1 RHUC is caused by a loss-of-function mutation in *SLC22A12*, which encodes the URAT1 uric acid transporter within the apical plasma membrane of the proximal tubule. Type 2 RHUC is related to a mutation in *SLC2A9* (or glucose transporter 9 [GLUT9]), which encodes GLUT9 in the apical and basolateral membranes of the proximal tubule (Figure 1). Type 1 RHUC is more common than type 2 RHUC, but the latter is more severe, with the lowest blood levels of uric acid (2–5). Both have been associated with a clinical syndrome of exercise-induced AKI. These are rare, autosomal-recessive, genetic mutations but can be tested with commercial, renal-oriented, genetic panels that are finding a rapidly expanding role in chronic kidney disease and unexplained AKI, as could have been the case here.

There are two theories that explain exercise-induced AKI seen in RHUC. One is renal tubular uric acid overload with crystal formation brought on by exercise, which increases protein catabolism and thus uric acid production. This increased protein catabolism will also lower the urine pH, which markedly decreases uric acid solubility. Finally, exercise may lead to dehydration and increase urinary concentration, which will further decrease uric acid solubility. These factors could lead to uric acid tubular obstruction and hematuria from crystal-induced damage. Uric acid stones have been occasionally described in RHUC. The second RHUC AKI hypothesis relates to the fact that uric acid has potent antioxidant activity, and this may be lacking in patients with RHUC. Supporting the former explanation—that exercise-induced AKI is a result of an increased uric acid load (exercise) in a dehydrated acidic urine—are the facts that a patient with RHUC and exercise-induced AKI underwent a formal physical fitness test, the uric acid excretion rate increased three-fold from 0.48 mg/min to 1.49 mg/min, and he developed AKI. The patient then received allopurinol, 300 mg/day, for 5 days; the physical fitness test was repeated; the uric acid excretion was lower at 0.28 mg/min and did not increase with exercise (0.22 mg/min); and the patient did not develop AKI (5). Whether there is a role for allopurinol in RHUC-associated AKI is unknown. There was additional discussion in the Communities thread for the use of urine alkalization with sodium bicarbonate, representing more speculation, but interesting nevertheless.

Although it is extremely unlikely that the average nephrologist will ever see a case of RHUC, and even though I find the purported mechanism of AKI associated with RHUC extremely interesting, I would emphasize that this is more than a fascinating case but demonstrates what an asset ASN Communities is to members of ASN. This is a lesson about how international collaboration not only helps a physician solve a mystery—and in doing so, potentially helps a patient—but in the process, also educates a broad "community" of nephrologists. ■

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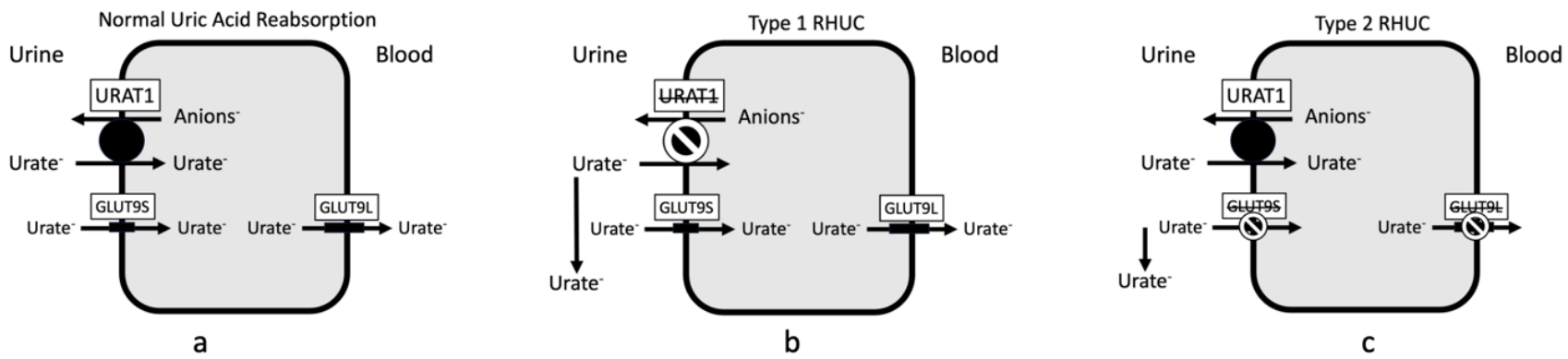
Figure 1. Normal uric acid reabsorption compared with type 1 and type 2 renal hypouricemia



Filtered uric acid is transported back into the blood by two mechanisms. There is an anion exchanger URAT1 on the apical side of the proximal tubule membrane that transports uric acid into the cell. It then exits the cell through the GLUT9 transporter, which exists as a long form (GLUT9L) located on the basolateral proximal tubule membrane and a short form (GLUT9S) located on the apical proximal tubule membrane (a). Defects in either URAT1 (b) or GLUT9 (c) will impair uric acid reabsorption and lead to hypouricemia, increasing the risk for uric acid stones and exercise-induced AKI.