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Acute Kidney Injury Related to Muscle Breakdown-Not All Due to Rhabdomyolysis: A Case of Acute Urate Nephropathy

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Abstract

A young man with a history of pseudo-seizures was admitted after an episode of severe agitation and rigorous physical activity. The patient was febrile on admission with notable leukocytosis and lactic acidosis but a negative infectious workup. During the hospitalization, the patient developed severe Acute Kidney Injury (AKI) despite fluid hydration. Creatinine Phosphoryl Kinase (CPK) was minimally elevated at 693 U/l. Urine microscopy was significant for many uric acid crystals. Subsequent lab studies revealed an elevated uric acid level of 13.4 mg/dl with fractional excretion of urate (Fe-Urate) of 13%. The patient was treated with rasburicase and allopurinol with the improvement of AKI that paralleled the improvement in hyperuricemia. AKI was likely due to acute urate nephropathy from a pseudo-seizure. AKI following an icteric activity or rigorous physical activity can occur via a mechanism that is independent of rhabdomyolysis. Acute Urate Nephropathy should be considered in cases with no significant elevations of CPK, with prompt initiation of rasburicase and potentially rapid resolution of AKI.

Keywords: Acute kidney injury • Leukocytosis • Heart failure

Introduction

A young male in his mid-twenties with a medical history of mild intellectual disability, depression with occasional episodes of pseudo-seizures and agitation, the most recent episode occurring about a month before admission. Workup during a recent hospitalization had been negative for infectious causes including Lyme's disease, Ehrlichiosis, HIV, and VDRL. Further seizure workup, including MRI brain and EEG, were insignificant. Urine screens for drugs of abuse were consistently negative. Current medications included Remeron, propranolol, and Seroquel. Asides from occasional periods of agitation and "shaking" episodes, his symptoms had significantly improved. However, he was admitted a month later to our center with an episode of severe agitation with pseudo-seizures, with onset on the morning of the presentation, this was associated with violent episodes necessitating the use of haloperidol and lorazepam.

Case Report

At presentation, he was febrile with a temperature of 38.9°C, had leukocytosis with a Total White Blood count (WBC) of 20.7 × 10^6, with an increased Absolute Neutrophil Count (ANC) of 18.9. He was initially admitted with concerns for an Infectious etiology. However, further evaluation including HIV, EBV was negative, with no growth from blood cultures. Other laboratory abnormalities included; Creatinine Phosphoryl Kinase (CPK) minimally elevated at 693 U/l, serum lactate of 7.03, Lactate Dehydrogenase (LDH)-282 U/L, and C-Reactive Peptide (CRP)-1.5 (Tables 1 and 2). Kidney function before admission was normal, with a baseline serum creatinine of 0.7-0.9. Creatinine on day 1 was 1.5. He had no change in measured urinary output. Urinalysis on admission showed Protein 2+ and moderate blood. He was resuscitated with 2 L of isotonic saline. Serum creatinine worsened to 3.8 on day 2 and then to 7.1 on day 3. Further workup was obtained as follows; FeNa 4%, FeUrea was 44.5%, suggestive of intrinsic renal injury. Repeat Urine dipstick showed protein 3+, moderate blood, and urine pH-5.5. A Nephrologist performed urine microscopy revealed Urine sediments with 3-5 isomorphic RBC/HPF, WBC> 50, and multiple uric acid crystals (Figure 1).

Semi-quantitative urine protein estimation was obtained, suggestive of severely increased albuminuria of UACR- 539.6 mg/g. Further workup for Rapidly Progressive Glomerulonephritis was warranted and the following tests were ordered as follows; hepatitis B and C (non-reactive), complements C3/C4, anti-GBM, anti-PR3, and anti-MPO. All of which were either negative or within normal limits. Serum uric acid level was requested based on urine sediments and was elevated at 13.4 mg/dl, with concerns for acute urate nephropathy, rasburicase 3 mg, was given on day 2 of admission. Serum creatinine improved to 6.1 on day 4, and by day 7 was 3.8. He was started on allopurinol 100 mg daily and continued IV hydration with isotonic fluid until day 7. Improvement of AKI paralleled improvement of uric acid, with a level of 4.3 a day after administration of rasburicase. He had no known familial disorders of urate metabolism, with these usually associated with earlier age of onset. Flow cytometry with a predominance of T Cells was nonspecific for a myeloproliferative disorder, and leukocytosis had resolved by day 3 of admission. The likely etiology of AKI was secondary to acute urate nephropathy, with the precipitating event being prolonged hyperactive agitation with muscle breakdown. He was continued on a course of allopurinol for 2 weeks until discharge, with his renal function returning to baseline about 3 weeks from the initial presentation.

Discussion

The end product of purine metabolism is uric acid, and increased cell turnover or cell destruction, both associated with increased purine metabolism are associated with increased levels of xanthine which is then oxidized to uric acid in the liver. Tumor lysis syndrome, with increased breakdown of cellular nucleic acid, is commonly associated with acute hyperuricemia, increased renal excretion of uric acid and the risk for Acute Kidney Injury (AKI) [1-3]. Rigorous exercise has been shown infrequently to increase uric acid levels, however, the Fe-Urate remains stable, probably demonstrating a potential compensatory mechanism [4,5]. Excessive muscular activity as seen with seizures can lead to the development of AKI due to increased muscular breakdown and rhabdomyolysis associated with toxic and tubular kidney damage [5]. Seizures are a rare cause of acute hyperuricemia. However, there are reported cases

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Table 1. Significant laboratory results on days 1 and 3 (LDH-Lactate Dehydrogenase).

Variables	Day 1	Days 2-7
Total WBC	20.7×10^6	8.57×10^6
Absolute Neutrophil count	18.90	5.62
LDH	--	282
Lactate	7.03	1.22
Serum creatinine	1.5	7.1
CPK	741	--
Urine Creatinine	--	75.7
Urine Uric acid	--	21.1
Fractional excretion of Urate	--	14.77
Random urine		
Uric acid	--	--
Creatinine	--	0.28
Urinalysis/Microscopy		
PH	6.0	5.5
SG	1.019	1.029
Protein	3+	1+
Blood	10-20	3-5
WBC (White Blood cell)	>50	few

CPK: Creatinine Phosphoryl Kinase; WBC: White Blood cells

Table 2. Uric acid and serum creatinine trends after rasburicase administration.

Serum Uric acid	13.4	After Rasburicase	11.6	6.8	4.3	2.4	1.6
Serum creatinine	7.1		6.8	6.1	5.1	4.3	3.8

of icteric episodes being associated with deleterious uric acid levels [6]. Proposed mechanisms for cellular breakdown with seizures include; increased oxygen demands because of increased catecholamines, and with prolonged episodes, increased risk of hypoxic tissues. Hyperuricemia is defined in men as SUA >6.5 mg/dl and 7 mg/dl in men and women respectively [7]. AKI secondary to acute urate nephropathy is classically associated with uric acid levels >12 mg/dl, via a crystal-induced mechanism; Monosodium Urate crystal deposition in Tubular epithelial cells leads to increased tubular and intrarenal pressures, as well congestion of renal venules via renal tubular obstruction from crystal deposition, which subsequently sets off an inflammatory cascade leading to fibrosis. The consequence of these is a decrease in GFR secondary to decreased renal blood flow as well as an increase in tubular pressure [2,3]. Likewise, soluble Uric acid may also stimulate an inflammatory response by activating NLRP3 inflammasome, with subsequent release of CXCL12 and HMGB1 in Tubular epithelial cells [3,8]. Soluble Uric acid also stimulates proinflammatory cytokines in the peripheral circulation [3]. This may explain the association of fever and leukocytosis seen in acute urate nephropathy.

Other Crystal-independent pathways have also been described and may even occur with serum uric acid levels <12 mg/dl. These mechanisms reduce GFR and renal blood flow by activation of the renin-angiotensin pathway, increased reactive oxygen species, inflammatory mediators (MCP-1, ICAM, CRP), as well as antiangiogenic properties inducing endothelial cell apoptosis and impaired renal autoregulation [1-7]. The patient with acute urate nephropathy has fever and leukocytosis due to systemic inflammatory response with cytokine release. Rigorous physical activity, even in the absence of true seizure activity can lead to tissue hypoxia. Lactic acidosis, as a result of tissue hypoxia, causes acidic urine which favors tubular precipitation of uric acid. Concomitant dehydration and hyperthermia also increase urine uric acid concentration. Lactic acidosis also reduces the tubular secretion of uric acid by a direct mechanism [9]. In a patient with hyperuricemia, random urine uric acid to creatinine ratio >1 is highly predictive of acute urate nephropathy and is useful in differentiating from other causes of AKI, where uric acid: Creatinine is <1 as a result of reduced uric acid secretion [10]. In this index case, a random urine uric acid was obtained after administration of rasburicase, and we obtained a ratio <1, which is most likely to reflect a response to therapy in this case. Oliguric AKI is the classical manifestation of acute urate nephropathy.

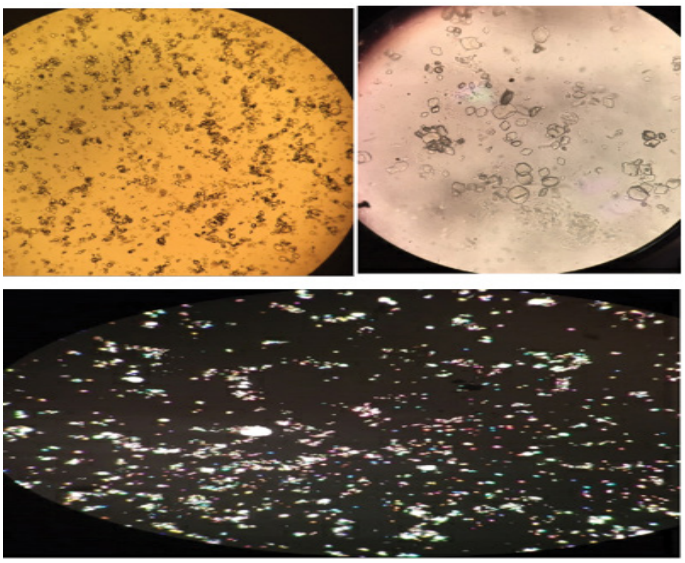

Figure 1. (A) Uric acid crystals under light microscopy, with numerous diamond-shaped crystals seen in (B) Polarized microscopy, (C) Demonstrates highly birefringent crystals.

This is likely due to crystal deposition and intraluminal obstruction. However, urine output may be preserved as with our patient, perhaps further illustrating the role of crystal-independent mechanisms in the development of AKI related to hyperuricosuria. Acute Urate nephropathy is potentially reversible if treatment is initiated early. Rasburicase rapidly oxidizes uric acid to the more soluble allantoin is effective in preventing the initiation of hemodialysis. Alkalization of urine also facilitates solubility of uric acid, reducing the risk of tubular precipitation. The patient, in this case, showed complete recovery of kidney function with Intravenous (IV) hydration with isotonic fluids improving diuresis, as well as with rasburicase.

Conclusion

This case highlights the need for Nephrologists to consider acute urate nephropathy as a differential diagnosis in patients with AKI after rigorous physical activities including seizures, especially in the absence of significant elevations in CPK. It emphasizes the role of thorough urine microscopy as part of the workup of an AKI. There may also be a role for a repeat random Uric acid to creatinine ratio evaluation after treatment, especially in cases where a transient etiology such as exercise or seizures is suspected.

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