Kidney Medicine

Glycosuria and Acute Kidney Injury: A Rare Presentation of Acute Interstitial Nephritis

Benjamin A. Schwartz and Jason M. Kidd

Acute interstitial nephritis (AIN) is often induced by drugs and is a common cause of acute kidney injury. Clinically diagnosing AIN can often be challenging because these signs and symptoms rarely present in concert. The inflammatory pathology of AIN leads to renal tubule dysregulation, which can be clinically observed as glycosuria, eosinophilia, leukocytes or white blood cell casts, and proteinuria. We present a case of an otherwise healthy woman in her 30s with AIN presenting with acute kidney injury and glycosuria without pyuria. This patient had an atypical presentation of AIN that lacked classic diagnostic laboratory features and has been rarely reported. She had profound glycosuria in the setting of normoglycemia, which resolved following a course of corticosteroids. Glycosuria was most likely due to proximal tubule damage from AIN. This case supports previous hypotheses that drug-induced AIN can cause proximal tubule dysfunction resulting in glycosuria in the absence of other identifiable proximal tubule dysregulations. We hypothesize that resolution of AIN involves the repair and restoration of sodium-dependent glucose cotransporter function.

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INTRODUCTION

Acute interstitial nephritis (AIN) is commonly caused by drugs and is a frequent cause of acute kidney injury (AKI). Antibiotics and nonsteroidal anti-inflammatory drugs are most often responsible.[1] The classic triad of AIN consists of eosinophilia, rash, and fever. However, clinically diagnosing AIN can often be challenging because these signs and symptoms rarely present in concert.[2] The inflammatory pathology of AIN can lead to renal tubule dysregulation, which can be clinically observed as glycosuria, phosphaturia, and aminoaciduria. Definitive diagnosis is made through kidney biopsy, which reveals interstitial inflammation with a lymphocytic predominance and eosinophils.[3] We present a case of AIN presenting with AKI and glycosuria without pyuria.

CASE REPORT

A woman in her 30s without a significant medical history presented to her primary care physician with a 2-week history of malaise and cough and was prescribed a course of amoxicillin for treatment of presumed tonsillitis. A month later, she developed nausea, vomiting, poor oral intake, abdominal pain, and shortness of breath. She presented to her primary care physician and was prescribed ciprofloxacin for possible diverticulitis. A basic metabolic panel was sent and was significant for a serum creatinine level of 6.9 mg/dL without antecedent history of AKI. She was then directed to the emergency department and subsequently admitted to the hospital.

On admission, the patient was afebrile with blood pressure of 169/104 mm Hg and pulse rate of 85 beats/min. Her examination was notable for trace edema of the lower extremities. She had no rashes or scleral icterus, cardiac and lung examination results were unremarkable, and abdominal examination results were benign.

Aside from AKI, the patient's laboratory results were significant for hypokalemia with a potassium level of 3.1 mmol/L and hemoglobin level of 11.7 g/dL. Glucose level was 119 mg/dL. Urinalysis results were significant only for glycosuria with glucose excretion > 500 mg/dL, ketonuria, and proteinuria (1+). Urine sediment was examined microscopically and was unremarkable without pyuria, red blood cells, or muddy brown casts. Hepatitis and HIV serologic test resuts were negative and complement levels were normal. Due to her glycosuria, serum and urine immunofixation were analyzed and were negative. She was noted to have an erythrocyte sedimentation rate of 55 mm/h. Ultrasound of the kidneys revealed increased cortical echogenicity without evidence of hydronephrosis or renal artery stenosis. Other laboratory results are shown in Table 1.

Following 48 hours of aggressive hydration, the patient's serum creatinine level improved to 5.8 mg/dL and urinary excretion was ~10 L. She had persistent glycosuria with normal serum glucose levels (Table 2). Because kidney function was slightly improving, kidney biopsy was deferred and she was discharged with close follow-up.

On presentation to the clinic 4 days later, the patient was noted to have continued nausea and poor oral intake. Serum creatinine test was repeated and the level was 5.8 mg/dL. Urinalysis was significant for continued glycosuria. She subsequently underwent kidney biopsy. Twenty-seven glomeruli were present on the sample and all were normocellular without evidence of sclerosis. The interstitium was infiltrated by mononuclear cells and many eosinophils with some intratubular red blood cell casts. Kidney tubules were nonatrophic. Immunofluorescence studies were negative for immunoglobulin A (IgA), IgG,

Table 1. Laboratory Values Before Admission, During Stay, and After Discharge

Time	Serum Creatinine, mg/dL	Serum Urea Nitrogen, mg/dL	Serum Glucose, mg/dL	Urinary Glucose, mg/dL
1 d before admission	6.94	53	94	Not assessed
Day 1	7.65	60	119	>500
Day 3	5.83	43	120	>500
4-d follow-up	5.82	44	103	150
1-wk follow-up	4.05	34	103	150
8-wk follow-up	1.33	19	120	50
10-wk follow-up	1.32	21	89	Negative
20-wk follow-up	1.18	15	85	Negative
1-y follow-up	0.96	11	85	Negative

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; serum urea nitrogen in mg/dL to mmol/L, ×0.357; glucose in mg/dL to mmol/L, ×0.05551

IgM, C1q, C3, albumin, and κ and λ, but were fibrinogen 3+/4 positive in the interstium (Fig 1). Although the patient initially presented with hypokalemia, this was not persistent during her clinical course. On initial presentation, she had a significant metabolic acidosis but at follow-up, bicarbonate level was 22 mmol/L (Table 3). Unfortunately, further evaluation was not performed to differentiate between tubular or glomerular proteinuria.

A diagnosis of AIN was made, and the patient was started on treatment with prednisone, 60 mg, daily. She began to show clinical improvement rapidly and the prednisone dosage was tapered off during the course of 4 weeks. Her glycosuria resolved after 1 month of therapy. Twelve months after her diagnosis, serum creatinine level was noted to be 0.96 mg/dL and she has no glycosuria.

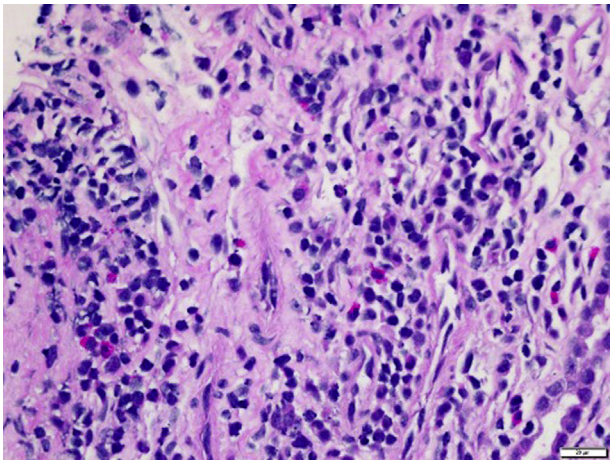

Figure 1. Hematoxylin and eosin staining of kidney biopsy specimen 3 weeks after onset of symptoms. The interstitium is infiltrated by mononuclear cells and many eosinophils without evidence of vasculitis.

Table 2. Urinalysis on Day 1 of Admission

Urine	Result	Reference Range
Creatinine, mg/dL	40.4	29-278
Sodium, mmol/L	38	28-272
Protein, mg/dL	36.3	25-50
Protein-creatinine, mg/mg	0.9	<0.2
pH	5.0	5-8
Ketones, mg/dL	20	<20

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4.

DISCUSSION

AIN is a common cause of AKI. Most cases are caused by drugs, followed by autoimmune disorders and infections.[4] It is often challenging to diagnose AIN due to the lack of clear-cut examination findings and laboratory abnormalities that signify interstitial kidney inflammation.[3] The clinical presentation of AIN often includes nausea, vomiting, malaise, rash, and fever. Laboratory findings associated with AIN may include increased plasma creatinine level, hematuria, pyuria with many leukocytes, white blood cell casts, and other urinary sediment abnormalities.[3] The diagnosis can be definitively confirmed by kidney biopsy, which reveals an interstitial infiltrate of lymphocytes, monocytes, and eosinophils with relatively spared glomeruli.

We suspect that this case was a drug-induced AIN due to amoxicillin taken before presentation. Drug-induced interstitial nephritis commonly manifests 2 to 40 days following drug exposure.[5] Beta-lactams are the most commonly cited drugs implicated in allergic reactions and are eliminated through glomerular filtration with some level of active transport within the tubular epithelial cells.[6] The pathogenesis of drug-induced AIN likely involves binding of the drug to tubular cells, acting as haptens, which then become immunogenic, causing damage to the tubules.[5]

This patient had an atypical presentation of AIN that has rarely been reported. She lacked classic features that would suggest a diagnosis of AIN, such as fevers, peripheral eosinophilia, and pyuria. In addition, our patient presented with glycosuria with normoglycemia, consistent with proximal tubule dysfunction. Glycosuria in the absence of classic features is an uncommon feature of AIN and has been rarely reported. Limuswat and Prabhakar[7] (2012) described a case of AIN related to nonsteroidal anti-inflammatory drug consumption with reversible glycosuria also in the absence of other classic features such as acidemia or significant aminoaciduria. The patient's glycosuria and AKI resolved with cessation of the drug therapy and administration of a course of corticosteroids.[7]

Physiologic excretion of glucose by the kidney in healthy adults is minimal. Sodium-dependent glucose cotransporters (SGLTs) within the proximal tubule are responsible for most glucose resorption. Pathologic glucose excretion commonly ensues after serum glucose

Table 3. Metabolic Panel and Urine Studies on Admission and at 1-Week Follow-up

	On Admission	1 wk Follow-up
Serum sodium, mmol/L	135	136
Serum potassium, mmol/L	3.1	3.7
Serum chloride, mmol/L	106	106
Serum bicarbonate, mmol/L	14	22
Serum urea nitrogen, mg/dL	60	34
Serum creatinine, mg/dL	7.65	4.05
Serum glucose, mg/dL	119	103
Serum phosphorus, mg/dL	4.0	2.6
Urine creatinine, mg/dL	40.4	42.1
Urine phosphorus, mg/dL	Not obtained	15.3
Urine potassium, mg/dL	Not obtained	48.1

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; serum urea nitrogen in mg/dL to mmol/L, ×0.357; glucose in mg/dL to mmol/L, ×0.05551.

levels exceed 200 to 350 mg/dL due to the capacity and saturation of glucose transporters within the tubules. Glycosuria can be caused by diabetes mellitus, gestational diabetes, and Fanconi syndrome. In diabetes mellitus, the serum glucose level exceeds the threshold of the SGLT, leading to glucose spillage in urine. Fanconi syndrome is characterized by proximal tubule dysfunction leading to glycosuria, aminoaciduria, and phosphaturia. Genetic disorders such as familial renal glucosuria cause isolated glycosuria with normoglycemia due to mutations within the SLC5A2 coding gene of SGLTs.[8] One must consider dysregulation of the proximal tubule when glycosuria exists without elevated serum glucose levels.

Interstitial nephritis can result in tubular damage causing proximal tubule dysfunction. This can manifest pathologically as electrolyte disturbances, phosphaturia, aminoaciduria, and other abnormalities. Our patient's glycosuria was most likely due to proximal tubule damage from AIN. Our patient also lacked typical laboratory findings associated with AIN. This case supports previous hypotheses that drug-induced AIN can cause SGLT dysfunction resulting in glycosuria. Due to reversibility of this glycosuria, it is likely that resolution of AIN involves the repair and restoration of SGLT function.

Standard of care for drug-related AIN involves an early diagnosis through kidney biopsy and elimination of the inciting drug. Due to the immunogenic nature of this disease, corticosteroid therapy is often used to alleviate kidney inflammation. In the past, there has been conflicting evidence on the efficacy and timing of corticosteroid therapy, but newer studies have shown benefit when corticosteroid therapy is started early and continued for at least 1 month, with further treatment tailored on response.[9] Further investigation into the pathophysiology of tubule disruption within drug-induced AIN and AKI is warranted to more effectively diagnose and more specifically treat this illness.

ARTICLE INFORMATION

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