

\xB2\xE9\xD6\xD8\xCE|\xFE/93976_Revi
sion_Auto_Edited -.docx

A case of severe acute kidney injury due to oxalate crystal deposition induced severe interstitial nephritis: A case report and literature review

Lathiya MK, Errabelli P *et al.* A case of severe acute kidney injury due to oxalate crystal deposition induced severe interstitial nephritis: A case report and literature review

Maulik K Lathiya, Praveen Errabelli, Sasmit Roy, Neeharik Mareedu

Abstract**BACKGROUND**

Acute kidney injury due to interstitial nephritis is a well-known entity. Interstitial nephritis can be acute or chronic, leading to acute kidney injury or chronic kidney disease depending on the duration of exposure to the offending agent and severity of insult [1, 2]. Interstitial nephritis usually occurs due to exposure to various drugs. The list of drugs available for interstitial nephritis is quite large. However, interstitial nephritis due to causes other than medications is uncommon [2]. Here, we describe a case of severe acute kidney injury due to interstitial nephritis triggered by intratubular oxalate crystal deposition and its management.

CASE SUMMARY

A 71-year-old female with obstructive sleep apnea, peripheral vascular disease, common iliac artery stenting, Guillain Barre syndrome, hypertension, and hyperlipidemia was admitted to the hospital with symptoms concerning stroke. She had progressive weakness in her lower extremities (reports left more than right), intermittent slurring of speech, dementia, decreased appetite, and severe fatigue. She

denied any dysuria, urinary frequency, urgency, or decreased urine output. She reported diarrhea for one week, 2 wk before admission, which was resolved without any medical intervention. She has been on 25 mg hydrochlorothiazide daily (for more than 2 decades) and 100 mg metoprolol succinate daily for her blood pressure. Her vital signs on admission were as follows: afebrile, heart rate approximately 70 beats/min, respiratory rate 16 breaths per minute, blood pressure 153/128 mmHg, and weight 76 kg.

Evaluation in the emergency room revealed severe acute kidney injury. She had normal kidney function at baseline as per the patient's previous baseline range, with a serum creatinine level of approximately 0.7 mg/dL and an estimated glomerular filtration rate (eGFR) greater than 60 mL/minute. The basic metabolic panel (BMP) on admission showed a creatinine concentration of 10 mg/dL and an eGFR concentration less than 15 mL/minute. She had moderate acidosis with an anion gap of 17, a serum bicarbonate concentration of 24 millimoles/L, a sodium concentration of 136 millimoles/L, a chloride concentration of 95 millimoles/L and a blood urea nitrogen (BUN) concentration of 69 mg/dL. Computed tomography (CT) of the abdomen pelvis did not reveal any hydronephrosis but showed a 3 mm (approximately 0.12 in) stone in the distal left ureter. A renal artery Doppler study revealed normal-sized kidneys bilaterally with normal velocities in both renal arteries and no occlusion in the renal arteries. Urinalysis on admission revealed large blood, 30 mg/dL protein, 4-10 white blood cell (WBC) counts per high-power field, no red blood cell (RBC) count, and no granular casts. The creatinine kinase level was 862 U/L. Her complete blood count (CBC) was 9.8 g/dL, her platelet count was 243,000/mL, and her leukocyte count was 6000/mL. She had severe hypokalemia; her potassium concentration was 2.7 millimoles/L at admission, and she received IV and oral potassium chloride (KCl) supplements. The magnesium concentration was 2.3 mg/dL.

She underwent extensive serology investigations for cryoglobulins, ANCA vasculitis, anti-GBM antibody disease, antinuclear antibody screening, monoclonal protein studies

to detect paraproteinemia, serum free light chains, viral hepatitis panels, and complement agents, which were all negative.

She received normal saline and potassium chloride supplementation and had a normal urine output. However, her renal function did not significantly improve. HCTZ was discontinued due to hypokalemia and acute kidney injury. She was started on Nifedipine and continued to use metoprolol. After 48 h (approximately 2 days) of continuous IV fluid infusion, her creatinine level remained at approximately 9 mg/dL, and her eGFR level remained below 15 mL/minute. A kidney biopsy was performed. A kidney biopsy revealed severe acute interstitial nephritis with deposits of oxalate crystals. There was no evidence of any immune complex deposits in the immunofluorescence study. Light microscopy revealed mild tubular interstitial scarring but severe diffuse interstitial edema involving the cortex and medulla and severe tubular epithelial cell injury with tubular lumens containing hypereosinophilic casts and multiple oxalate crystals. The interstitial tissue contained dense infiltrates of lymphocytes and eosinophils. Electron microscopy revealed normal cellularity and mildly expanded mesangial regions with no immune complex or paraprotein-related deposits. The glomeruli are non-proliferative, and the tubular interstitial compartment shows interstitial edema with severe inflammation. There was glomerular basement membrane wrinkling on several segments and no tubular basement membrane deposits.

She denied any exposure to nonprescription medication, such as proton pump inhibitors or NSAIDs and herbal agents, which can cause interstitial nephritis. She was on hydrochlorothiazide and metoprolol for hypertension for more than 20 years. Because of her severe hypokalemia and AKI, HCTZ was discontinued. She started prednisolone (60 mg daily) for acute interstitial nephritis. She was discharged with trimethoprim-sulfamethoxazole for *Pneumocystis pneumonia* (PCP) prophylaxis and calcium and vitamin D supplements for preventing osteoporosis from high-dose steroids.

Repeating BMP after one month showed that her serum creatinine concentration improved to 1.5 mg/dL, and her eGFR was close to 35 mL/minute. Her prednisolone dose slowly tapered over 6 wk (approximately 1 and a half months). Her potassium concentration stabilized, and she was given potassium supplements at the follow-up visit. Repeat urinalysis did not reveal any WBCs, RBCs, or proteins. Blood pressure had normalized and was hovering at approximately 120 to 130/70 to 80 mmHg during the clinic visits.

The etiology of her acute interstitial nephritis, as determined by a pathologist, was due to a severe inflammatory reaction in the interstitial tissue surrounding multiple oxalate crystal deposits in the tubules. She did not have any history of renal calculi. However, CT of the abdomen and pelvis revealed ureteral calculi and biopsy also revealed oxalate crystals in multiple tubules. This is a unique case of crystal nephropathy.

CONCLUSION

4. Conclusion:

It is important to fully assess the impact of oxalate crystal deposition on renal function to provide comprehensive patient care. The frequency of interstitial nephritis due to oxalate crystal deposition, especially in the context of long-term thiazide diuretic use in the absence of other risk factors for interstitial nephritis, highlights the importance of a comprehensive diagnostic approach. This case contributes to the expanding body of knowledge on renal pathology, highlighting the clinical importance of identifying and addressing uncommon causes of interstitial nephritis. Further research and case studies will play an important role in improving our understanding of such unusual presentations and optimizing treatment strategies.

Key Words: Acute kidney injury; interstitial nephritis; oxalate crystal; hydrochlorothiazide; hypokalemia

¹
Lathiya MK, Errabelli P, Roy S, Mareedu N. A case of severe acute kidney injury due to oxalate crystal deposition induced severe interstitial nephritis: A case report and literature review . *World J Nephrol* 2024; 0(0): 93976
URL: <https://www.wjgnet.com/2220-6124/full/v0/i0/93976.htm>
DOI: <https://dx.doi.org/10.5527/wjn.v0.i0.93976>

Core Tip: We have submitted a case report detailing a rare instance of acute kidney injury presenting as interstitial nephritis due to oxalate crystal deposition. While cases of thiazide-induced interstitial nephritis are documented, occurrences after 20 years of treatment are uncommon. This underscores the necessity of considering oxalate crystal deposition when evaluating patients on long-term thiazide diuretics without other risk factors for interstitial nephritis, emphasizing the importance of a comprehensive diagnostic approach.

INTRODUCTION

Acute kidney injury due to interstitial nephritis is a well-known entity. Interstitial nephritis can be acute or chronic, leading to acute kidney injury or chronic kidney disease depending on the duration of exposure to the offending agent and severity of insult ^[1, 2]. Interstitial nephritis usually occurs due to exposure to various drugs. The list of drugs available for interstitial nephritis is quite large. However, interstitial nephritis due to causes other than medications is uncommon ^[2]. Here, we describe a case of severe acute kidney injury due to interstitial nephritis triggered by intratubular oxalate crystal deposition and its management.

CASE PRESENTATION

Chief complaints

Progressive weakness in lower extremities, intermittent slurring of speech, dementia, decreased appetite, severe fatigue.

History of present illness

A 71-year-old female presented with stroke-like symptoms including weakness, speech difficulties, and cognitive impairment. She reported a recent episode of diarrhea but denied urinary symptoms including dysuria, urinary frequency, urgency, or decreased urine output. She reported diarrhea for one week, 2 wk before admission, which was resolved without any medical intervention. She has been on 25 mg hydrochlorothiazide daily (for more than 2 decades) and 100 mg metoprolol succinate daily for her blood pressure.

Additional Comments: She denied any exposure to nonprescription medication, such as proton pump inhibitors or NSAIDs and herbal agents, which can cause interstitial nephritis. She was on hydrochlorothiazide and metoprolol for hypertension for more than 20 years. Because of her severe hypokalemia and AKI, HCTZ was discontinued. She started prednisolone (60 mg daily) for acute interstitial nephritis. She was discharged with trimethoprim-sulfamethoxazole for *Pneumocystis pneumonia* (PCP) prophylaxis and calcium and vitamin D supplements for preventing osteoporosis from high-dose steroids.

History of past illness

History of obstructive sleep apnea, peripheral vascular disease, common iliac artery stenting, Guillain Barre syndrome, Long-standing hypertension managed with hydrochlorothiazide (HCTZ) and metoprolol succinate, and hyperlipidemia. No history of renal calculi.

Personal and family history

No relevant family history.

Physical examination

Afebrile, heart rate approximately 70 beats/min, respiratory rate 16 breaths per minute, blood pressure 153/128 mmHg, and weight 76 kg.

Laboratory examinations

She had normal kidney function at baseline as per the patient's previous baseline range, with a serum creatinine level of approximately 0.7 mg/dL and an estimated glomerular filtration rate (eGFR) greater than 60 mL/minute. The basic metabolic panel (BMP) on admission showed a creatinine concentration of 10 mg/dL and an eGFR concentration less than 15 mL/minute. She had moderate acidosis with an anion gap of 17, a serum bicarbonate concentration of 24 millimoles/L, a sodium concentration of 136 millimoles/L, a chloride concentration of 95 millimoles/L and a blood urea nitrogen (BUN) concentration of 69 mg/dL.

Urinalysis on admission revealed large blood, 30 mg/dL protein, 4-10⁵ white blood cell (WBC) counts per high-power field, no red blood cell (RBC) count, and no granular casts. The creatinine kinase level was 862 U/L. Her complete blood count (CBC) was 9.8 g/dL, her platelet count was 243,000/mL, and her leukocyte count was 6000/mL. She had severe hypokalemia; her potassium concentration was 2.7 millimoles/L at admission, and she received IV and oral potassium chloride (KCl) supplements. The magnesium concentration was 2.3 mg/dL.

She underwent extensive serology investigations for cryoglobulins, ANCA vasculitis, anti-GBM antibody disease, antinuclear antibody screening, monoclonal protein studies to detect paraproteinemia, serum free light chains, viral hepatitis panels, and complement agents, which were all negative.

Repeating BMP after one month showed that her serum creatinine concentration improved to 1.5 mg/dL, and her eGFR was close to 35 mL/minute. Her prednisolone dose slowly tapered over 6 wk (approximately 1 and a half months). Her potassium concentration stabilized, and she was given potassium supplements at the follow-up visit. Repeat urinalysis did not reveal any WBCs, RBCs, or proteins. Blood pressure had normalized and was hovering at approximately 120 to 130/70 to 80 mmHg during the clinic visits.

Kidney Biopsy:

Final diagnosis: Acute onset of severe interstitial nephritis.

Light Microscopy: The glomeruli were normal in size and had a normal mesangial matrix. There was no mesangial or endocapillary hypercellularity. Special stains do not demonstrate spikes, craters, or basement membrane remodeling.

TUBULES AND INTERSTITIUM: Severe diffuse interstitial edema involving the cortex and medulla was observed. Severe tubular epithelial cell injury occurs with luminal ectasia, fraying of the brush border, and simplification of the lining epithelium. Tubular lumina contain necrotic debris, and some lumina contain hypereosinophilic rope casts. The interstitium contains dense infiltrates of lymphocytes. Some areas contained aggregates of eosinophils. Mild tubulitis was observed. There are intratubular oxalate crystals.

VESSELS: The visualized arteries show severe intimal fibrosis. There was no vasculitis, thrombi, or atheroembolic lesions.

Electron Microscopy: Normal cellularity and mildly expanded mesangial regions were confirmed. No immune complex or paraprotein-related deposits were observed, and the glomerular basement membranes showed wrinkling of several of the segments; however, other regions showed no ultrastructural abnormalities. There was mild foot process effacement present. An examination of the tubulointerstitial compartment revealed interstitial edema, severe interstitial inflammation, and multifocal tubulitis. No tubular basement membrane deposits were observed.

Impression: Kidney, needle biopsy: Acute interstitial nephritis.

Immunofluorescence: There was no significant glomerular staining for albumin, IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, or lambda light chains. The cast was observed to be stained equally with IgA, kappa, and lambda light chains.

Imaging examinations

Computed tomography (CT) of the abdomen/pelvis did not reveal any hydronephrosis but showed a 3 mm (approximately 0.12 in) stone in the distal left ureter. A renal artery

Doppler study revealed normal-sized kidneys bilaterally with normal velocities in both renal arteries and no occlusion in the renal arteries.

FINAL DIAGNOSIS

Severe acute interstitial nephritis with oxalate crystal deposits leading to acute kidney injury.

TREATMENT

She received normal saline and potassium chloride supplementation and had a normal urine output. However, her renal function did not significantly improve. HCTZ was discontinued due to hypokalemia and acute kidney injury. She was started on Nifedipine and continued to use metoprolol. After 48 h (approximately 2 days) of continuous IV fluid infusion, her creatinine level remained at approximately 9 mg/dL, and her eGFR level remained below 15 mL/minute.

OUTCOME AND FOLLOW-UP

Serum creatinine and eGFR improved with prednisolone treatment. Potassium stabilized, blood pressure normalized, and urinalysis normalized. Prednisolone tapered over 6 wk. Follow-up showed continued improvement in renal function and resolution of symptoms. Biopsy confirmed oxalate crystal deposits as the etiology of acute interstitial nephritis.

DISCUSSION

Interstitial nephritis is a renal disease characterized by inflammation and scarring of the kidney's tubular and interstitial components. It manifests in three primary types: immune-mediated, infection-mediated, and idiopathic. Immune-mediated interstitial nephritis can be caused by drug reactions or due to immunological diseases. Many drugs, including antibiotics, antacids, analgesics, immunotherapies, diuretics (including thiazide diuretics), antivirals, anticonvulsants, lithium, allopurinol, *etc.*, have been

linked to interstitial nephritis [2]. The mechanism through which drugs induce interstitial nephritis varies [3]. As mentioned, drug-induced interstitial nephritis is a well-documented entity associated with thiazide diuretics, and our case report adds a complex layer to this well-known entity [1, 2, 4].

In our patient, the complexity was enhanced when multiple oxalate crystals were identified *via* kidney biopsy along with interstitial nephritis. Oxalate nephropathy is a rare pathology that can be difficult to diagnose clinically and requires a biopsy. This presentation aligns with crystalline nephropathy, a condition marked by crystal precipitation in kidney tubules [2, 3]. Crystalline nephropathy poses risks of both acute and chronic kidney injuries. Various factors contribute to the risk of crystal deposition, encompassing intravascular volume depletion, underlying kidney disease, and metabolic imbalances that alter urinary pH [2, 3]. The intricate interplay of supersaturation, urine pH, and crystallization inhibitors influences intratubular crystal deposition. Drug-induced crystal precipitation, often associated with supersaturation in low urine volume or drug insolubility in acidic or alkaline urine pH, can exacerbate renal complications. Metabolic disturbances, including systemic acidosis or alkalosis and renal tubular acidosis, play a role in worsening intrarenal crystal deposition. Patient characteristics linked to medication intake predispose individuals to intratubular crystal deposition and subsequent tubular obstruction [2, 3].

Severe volume depletion, prevalent in conditions such as chronic diarrhea, anorexia, excessive diuresis, febrile illnesses, adrenal insufficiency, and renal salt wasting, is a crucial factor in the development of acute kidney injury (AKI). Conditions leading to effective intravascular volume depletion, such as pancreatitis, ascites, heart failure, pleural effusions, and nephrotic syndrome, contribute to renal hypoperfusion, heightening the risk of tubular crystal deposition [2, 3]. Urine pH further modulates crystallization, with certain drugs exhibiting varying solubilities in acidic or alkaline urine. Crystal precipitation within the kidneys obstructs ³ tubular lumens in the distal

nephron, involving crystals mixed with cellular debris and proteinaceous material (10,11). Gastrointestinal disorders involving small bowel dysfunction or defective fat and bile acid absorption contribute to enteric hyperoxaluria, which is characterized by increased gastrointestinal oxalate absorption and excessive urinary oxalate excretion [2, 3]. In addition, certain case reports have shown an evidence, though rare, of food induced oxalate crystallopathy including excessive consumption of cashew nuts, vitamin C supplementation, spinach and peanuts [12].

Numerous case reports have described drug-induced crystallopathy [4-8]. In our case, the patient had been on a thiazide diuretic for more than two decades without any previous kidney injury or associated complications. The continued exposure to a thiazide diuretic throughout the period during which she had diarrhea raises the possibility of severe volume depletion and enteric hyperoxaluria as contributing factors to her crystal formation. Prolonged exposure to thiazide diuretics without any adverse events ruled out the possibility that interstitial nephritis was solely due to the thiazide diuretic. However, it is quite possible that thiazide diuretic use in the setting of diarrhea might aggravate volume depletion, leading to oxalate crystal deposition, which triggers the onset of interstitial nephritis.

Recommendations to reduce the risk of developing crystal nephropathy emphasize maintaining adequate volume status and avoiding concurrent use of diuretics, ACEIs, ARBs, and NSAIDs [2, 3]. In cases where crystal nephropathy occurs, sustaining a high urine flow rate is crucial for minimizing further crystal precipitation and dislodging obstructing crystals. Early detection and withdrawal of the causative agent can be achieved through timely examination of urine sediment in individuals experiencing AKI, which can sometimes demonstrate crystals. Monitoring facilitates the implementation of supportive measures, including volume repletion, urine alkalization and, rarely, hemodialysis, in severe cases of AKI [2, 3]. Case reports have highlighted various treatments for oxalate crystallopathy, often tailored to underlying

causes. For food-induced crystallopathy, a low-oxalate diet, high fluid intake, and calcium acetate have shown efficacy [12]. Treatment for oxalate disorders depends on whether they're primary or secondary. Enteric hyperoxaluria patients benefit from a low-fat, low-oxalate diet. Those with fat malabsorption may need calcium supplements or pancreatic enzyme supplementation (in case of pancreatic insufficiency). Lanthanum carbonate shows promise for secondary hyperoxaluria. Primary hyperoxaluria (PH) requires strategies to reduce endogenous oxalate production, with PH1 patients possibly benefitting from pyridoxine supplementation. Dialysis is essential if renal function declines, with transplantation preferred for severe systemic oxalosis in PH patients. In severe cases requiring dialysis, high flux or continuous hemodialysis is crucial for removing excess oxalate [13].

In this case, we treated the patient with a prolonged prednisolone tapering agent *via* a strategy targeting the inflammatory response associated with interstitial nephritis. There was a significant improvement in renal function, which provides insight into the role of corticosteroids in the treatment of oxalate crystallography-induced interstitial nephritis.

In addition, oxalate crystal deposition is associated with kidney epithelial cell damage, suggesting that crystals induce epithelial injury and progressive inflammation, leading to interstitial nephritis [9]. Our case study revealed that prolonged exposure to diuretics can lead to volume depletion, triggering oxalate crystal deposition, which can induce severe interstitial nephritis.

CONCLUSION

It is important to fully assess the impact of oxalate crystal deposition on renal function to provide comprehensive patient care. The frequency of interstitial nephritis due to oxalate crystal deposition, especially in the context of long-term thiazide diuretic use in the absence of other risk factors for interstitial nephritis, highlights the importance of a comprehensive diagnostic approach. This case contributes to the expanding body of

knowledge on renal pathology, highlighting the clinical importance of identifying and addressing uncommon causes of interstitial nephritis. Further research and case studies will play an important role in improving our understanding of such unusual presentations and optimizing treatment strategies.

ACKNOWLEDGEMENTS

The authors are very appreciative of the reviewers for their valuable feedback during review which helped us improve the article and publishers of the journal for publishing our article.

ORIGINALITY REPORT

5%

SIMILARITY INDEX

PRIMARY SOURCES

1	www.preprints.org Internet	69 words — 2%
2	www.ncbi.nlm.nih.gov Internet	44 words — 1%
3	www.tandfonline.com Internet	14 words — < 1%
4	Fernando C. Fervenza. "A Patient with Nephrotic-Range Proteinuria and Focal Global Glomerulosclerosis", Clinical Journal of the American Society of Nephrology, 2013 Crossref	12 words — < 1%
5	drbronquio.files.wordpress.com Internet	12 words — < 1%
6	f6publishing.blob.core.windows.net Internet	12 words — < 1%