Nitrofurantoin-Associated Acute Granulomatous Interstitial Nephritis

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Abstract
We report the case of a 71-year-old female who was incidentally found to have nonoliguric acute kidney injury on a routine workup for new-onset visual hallucination. Further history revealed inadvertent usage of nitrofurantoin for 3 months for an anticipated urological procedure. Renal biopsy demonstrated acute granulomatous interstitial nephritis. The renal function significantly improved following discontinuation of nitrofurantoin and corticosteroid administration. We highlight a rare association of nitrofurantoin with acute granulomatous interstitial nephritis through this case report.

Keywords
nitrofurantoin, acute interstitial nephritis, granulomatous interstitial nephritis, acute kidney injury

Introduction
Acute interstitial nephritis (AIN) is one of the common causes of acute kidney injury (AKI) and is associated with the presence of inflammatory infiltrates within the renal interstitium. AIN has been associated with 15% to 27% of patients with kidney dysfunction. However, the true incidence of AIN remains largely unrecognized as biopsy might not be sent in cases of clinical suspicion, and milder cases of AIN go undetected. There are many causes of AIN, with drug-induced AIN being the most common cause accounting for approximately 70% of all cases. Granulomatous interstitial nephritis (GIN) is a rare pathological feature seen in only 0.5% to 0.9% of all kidney biopsies. Although nitrofurantoin is a common cause of AIN, GIN is a rare entity. To our knowledge, there are only 2 case reports in the literature describing this condition. The knowledge of GIN is primarily based on case reports and case series. We present a case of a 71-year-old female with AKI found to have acute GIN on renal biopsy attributed to nitrofurantoin use.

Case Presentation
A 71-year-old female with a past medical history of multiple sclerosis and stress incontinence secondary to cystocele initially presented to her primary care physician with complaints of worsening lower extremity spasms and a new-onset visual hallucination. Routine basal metabolic panel performed for her symptoms incidentally revealed acute renal failure with a serum creatinine of 8.18 mg/dL. She was referred to the nearby hospital where she received 2-L boluses followed by maintenance intravenous fluids without significant improvement of kidney function. The patient was subsequently transferred to our institution for further workup and evaluation by nephrology. The patient’s baseline renal function was reportedly normal 3 months ago. She denied fever, chills, shortness of breath, skin rash, decreased urination, and other urinary symptoms on presentation. She was on long-term amantadine for fatigue related to multiple sclerosis. The patient used to follow-up with an urologist in Arizona for stress incontinence. She was scheduled to undergo an elective urological procedure for stress incontinence and was instructed to take nitrofurantoin 100 mg twice daily for 7 days before the procedure for presumed urinary tract infection (UTI). However, due to the coronavirus disease 2019 pandemic, her elective procedure was canceled, but she continued to take nitrofurantoin 100 mg twice daily for over 3 months for unknown reason. Clinical examination was remarkable for lethargy and altered mental status. Lungs were clear to auscultation bilaterally. The patient was afebrile, and vitals were within normal limits.

Laboratory workup confirmed AKI with a serum creatinine of 7.6 mg/dL and blood urea nitrogen of 60 mg/dL.

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Urine microscopy was bland without white blood cell, red blood cell, or protein, and urine cultures were negative for infection. Urine protein/creatinine ratio was 0.20 mg/mg. Liver function tests and serum albumin were within normal limits. Complete blood count demonstrated elevated absolute eosinophil count (1.8 × 10³/µL). The serial laboratory tests and reference range are detailed in Table 1. Renal ultrasound was unremarkable with no evidence of renal calculi or hydronephrosis. Further workup including vasculitic screening, autoimmune panel, serum immunoglobulins, serum protein immunoelectrophoresis, complement level, hepatitis B and C, and parathyroid hormone level returned normal.

Despite stopping nitrofurantoin during admission, the patient’s creatinine remained elevated around 7.5 mg/dL, and nephrology was consulted. The patient exhibited features of uremia such as decreased appetite, nausea, and asterixis, warranting renal replacement therapy as per nephrology recommendation. The patient underwent 2 sessions of hemodialysis on day 4 and day 5 of admission and a percutaneous renal biopsy on day 4 to evaluate for etiology of renal failure. Renal biopsy revealed a moderately intense inflammatory infiltrate comprising predominantly of lymphocytes and histiocytes that were admixed with multifocal clusters of eosinophils and few plasma cells (Figure 1). Renal interstitium demonstrated a few scattered noncaseating granulomas with multinucleated giant cells consistent with acute GIN (Figures 2 and 3). There was mild to moderate interstitial fibrosis and tubular atrophy, admixed with interstitial edema, patchy acute tubular necrosis, and congestion of peritubular capillaries. Glomeruli were normal by light microscopy and immunofluorescent, and electron microscopy was negative for immune-complex deposits in the glomeruli. A Ziehl-Neelsen stain for acid-fast bacilli and Gomori methenamine silver stain for fungus was negative. Further testing included angiotensin-converting enzyme level, and the QuantiFERON tuberculosis test returned negative. Computed tomography scan of thorax and abdomen showed incidental small scarring, granulomas, and calcification in the right lung, intrathoracic lymph nodes, and spleen. Although the patient did not have known history of histoplasmosis, as per the infectious disease recommendation, those incidental findings were deemed to be secondary to old resolved histoplasmosis, which the patient might not have been aware of and did not warrant further evaluation and treatment in the absence of pulmonary or constitutional symptoms.

The patient was started on prednisone 60 mg on day 4 of admission with resultant significant improvement of her renal function, creatinine 2.8 mg/dL at discharge (Table 1). The patient’s visual hallucinations were attributed to amantadine toxicity from decreased renal excretion, which was gradually tapered and stopped leading to a subsequent visual hallucination resolution. The patient was discharged on a 30-day steroid taper with an outpatient nephrology follow-up. The patient’s most recent renal function test after 2 months showed a serum creatinine of 1.71 mg/dL. She has remained stable from nephrology standpoint.

| Laboratory values (units) | Day 1 | Day 7 | Day 14 | Day 16 | Reference ranges |
|--------------------------|-------|-------|--------|--------|------------------|
| Sodium (mmol/L)          | 140   | 139   | 143    | 144    | 136-145          |
| Potassium (mmol/L)       | 4.5   | 4.0   | 3.5    | 3.8    | 3.4-5.1          |
| Chloride (mmol/L)        | 108   | 101   | 101    | 106    | 98-107           |
| Bicarbonate (mmol/L)     | 18    | 27    | 26     | 26     | 22-29            |
| Blood urea nitrogen (mg/dL) | 60    | 58    | 54     | 39     | 8-23             |
| Creatinine (mg/dL)       | 7.64  | 4.76  | 3.16   | 2.58   | 0.7-1.2          |
| Glucose (mg/dL)          | 109   | 167   | 115    | 138    | 70-140           |
| Calcium (mg/dL)          | 8.4   | 8.3   | 8.0    | 8.7    | 8.8-10.2         |
| WBC count (10 × 3/µL)    | 8.4   | 14.1  | 15.1   | Not obtained | 4-10 |
| Hemoglobin (g/dL)        | 9.5   | 10.4  | 9.5    | Not obtained | 13.5-18 |
| Platelets (10 × 3/µL)    | 309   | 121   | 245    | Not obtained | 150-400 |
| Absolute eosinophil count (10 × 3/µL) | 1.48  | 0.01  | 0.21   | Not obtained | 0-0.5 |
Discussion

The clinical features associated with AIN are fever, rash, arthralgia, oliguria, and laboratory features include eosinophilia, proteinuria, and leukocyturia. Although our patient did not have all the systemic features associated with AIN, the presence of peripheral eosinophilia and a history of prolonged nitrofurantoin use were clinical clues that led to suspicion of AIN. The renal pathology further confirmed the diagnosis of AIN with granulomas. Moreover, the patients with granulomatous AIN tend to relatively lack the typical systemic manifestation as compared with the nongranulomatous counterpart.

Other causes of GIN excluding drugs include sarcoidosis, tuberculosis, fungal infections, and tubulointerstitial interstitial nephritis with uveitis. In our case, the special stains for fungus and tuberculosis were negative, which ruled out infectious causes. Even though there was an incidental finding of calcified granulomas in the lungs and spleen, the acute GIN was considered a separate process given the temporal association with nitrofurantoin use and improvement of renal function after discontinuation of nitrofurantoin and steroid administration. Sarcoidosis was considered as one of the differentials in our patient with noncaseating granulomas. However, the renal biopsy, showing the presence of eosinophilic infiltrate with peripheral eosinophilia, absence of pulmonary symptoms, normal serum calcium, and normal angiotensin-converting enzyme, made the diagnosis unlikely.

The drug-induced AIN is believed to be pathologically associated with the immunological process given its association with features of hypersensitivity and the fact that only a few patients exposed to a particular drug develop AIN, with a tendency of recurrence after repeat exposure to the drug. The pathogenesis for the development of epithelioid granulomas is not well understood in drug-induced interstitial nephritis. Still, it has been attributed to a delayed-type hypersensitivity reaction, and cell-mediated type 1 helper T cells response. The definitive diagnosis of AIN is made by renal biopsy, which characteristically shows interstitial edema, interstitial infiltrates predominantly composed of macrophages, plasma cells, and eosinophils. In our patient, it was unclear if the patient was taking nitrofurantoin for presumed UTI or recurrent UTI as the patient used to follow-up with urologist in Arizona and the records were not readily available and the patient herself was not aware of the situation. It is also unclear why the prescription was written in such a way that would allow her to refill the medication for more than 3 months.

The mainstay management of acute drug-induced GIN is the discontinuation of the offending agent. No therapeutic trials exist to assess the efficacy of steroids. In 2 such cases of acute nitrofurantoin–associated GIN reported by Korzets et al and Namagondlu et al, the renal function recovered with the withdrawal of nitrofurantoin alone without administration of corticosteroids. In their retrospective study, González et al noted that the delayed onset of steroid treatment was associated with the risk of incomplete renal recovery, suggesting early administration of steroid treatment might be essential in patients with drug-induced AIN. Similarly, in another retrospective study, Joss et al reported that administration of a moderate dosage of steroids was...
associated with a favorable prognosis in GIN irrespective of the underlying etiology and the degree of interstitial fibrosis. Nevertheless, our patient had significant renal function improvement with the early administration of steroids as soon as the diagnosis of AIN was confirmed.

**Conclusion**

With this case report, we would like to report a rare association of acute GIN with nitrofurantoin use successfully treated with the withdrawal of this agent and corticosteroid administration. We want to reiterate the importance of drug-induced interstitial nephritis in AKI and the role of early renal biopsy on establishing the diagnosis of AIN.

**Declaration of Conflicting Interests**

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**Ethical Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed Consent**

Informed consent for patient anonymized information to be published in this article was not obtained from the patient because our institution does not require informed consent for individual case reports.

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