

# Acute Interstitial Nephritis Induced by Clozapine

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## Abstract

Acute interstitial nephritis (AIN) classically presents as acute kidney injury most often induced by offending drugs. Less frequently it is secondary to infections, autoimmune disorders, or idiopathic conditions. Development of drug-related AIN is not dose dependent and a recurrence can occur with re-exposure to the drug. We present a 50-year-old male with treatment resistant schizoaffective disorder who developed clozapine-induced AIN, confirmed with kidney biopsy within 2 months of taking this medication. His kidney function improved with removal of the drug and treatment with steroids. However, his kidney function was again significantly impaired when rechallenged with even a lower dose of clozapine a year later. Kidney function returned to baseline after stopping clozapine. Monitoring of kidney function during clozapine therapy is essential to therapy. Prompt diagnosis is imperative as discontinuation of offending agent can prevent acute kidney injury.

**Keywords:** Acute interstitial nephritis; Clozapine; Refractory schizophrenia; Acute kidney injury; Drug reactions; Kidney biopsy; Schizophrenia

## Introduction

Clozapine has superior efficacy in treating refractory schizo-

phrenia in comparison to other antipsychotic medications [1]. Common side effects of clozapine include weight gain, constipation, oversedation, orthostatic hypotension, and sialorrhea [2]. Acute interstitial nephritis (AIN) is a very rare side effect of clozapine and has been reported rarely in the literature. It is often unrecognized in the early stages because of its asymptomatic nature but it can be life-threatening. We describe a case of AIN caused by clozapine that was confirmed by the kidney biopsy and reoccurrence of acute kidney injury (AKI) in 1 year later with rechallenge.

## Case Report

### Investigations

A 50-year-old male with a known history of schizoaffective disorder and bipolar disorder was admitted to the inpatient psychiatry unit with uncontrolled psychosis. The patient had grandiose delusions, referential delusions, thought broadcasting, and delusional perception. The psychosis has been getting worse 4 - 6 weeks before admission despite being compliant with psychotropic medications. The patient was diagnosed with schizoaffective and bipolar disorder at the age of 30. The patient has been treated before with both typical, atypical antipsychotic agents and mood-stabilizing agents which include chlorpromazine, fluphenazine, haloperidol, perphenazine, aripiprazole, risperidone, paliperidone, olanzapine, valproic acid, and lithium. Some of these agents have been given in long-acting injectable routes. Despite medication trials, intensive community support, assisted living facility placements, the patient's illness remained resistant to treatment which led to frequent and prolonged hospitalizations.

His past medical history is also significant for essential hypertension. His medications at the time of admission included paliperidone 12 mg daily, sodium valproate 500 mg in the morning, 1,000 mg at bedtime, lithium carbonate 300 mg twice daily, benztropine 0.5 mg twice daily, and amlodipine 10 mg daily. The patient was staying at the assisted living facility before admission. The patient had no prior history of smoking, alcohol use, or recreational drug use. The patient was divorced and had no family history of psychiatric illness.

The vitals on the admission were a temperature of 36.9 °C, pulse rate of 80 beats per minute (bpm), blood pressure of 135/80 mm Hg, respiratory rate of 18 breaths per minute. The physical examination was suggesting an anxious and confused

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person, but the rest of the physical examination was unremarkable. The psychiatric evaluation revealed that the speech was rapid, with intact language functioning, euphoric with manic affect. The thought process was significant for loose associations and paranoia.

## Diagnosis

The labs on the first admission are shown in Table 1. The patient was started on clozapine 25 mg daily and the dose was up titrated to 300 mg daily gradually over 2 weeks. Lithium was continued at the same dose and the rest of the anti-psychotics were stopped. The patient's psychosis improved significantly, and he was discharged to assisted living. The patient was readmitted back to the inpatient psychiatry unit in 5 days with fatigue, fever, and sweating. The vitals revealed temperature 38.6 °C, pulse rate of 110 bpm, blood pressure 140/90 mm Hg, respiratory rate of 24 breaths per minute. Physical examination revealed an ill-appearing individual, while the rest of the systemic examination was not significant. No rigidity or fluctuating consciousness was noted.

The labs on the second visit are depicted in Table 1. Notable serum finding was elevated serum clozapine level of 506 ng/mL. The patient was symptomatically treated for fever and was discharged on a decreased dose of clozapine 150 mg daily. Lithium was continued at the same dose.

The patient was readmitted again to the medical floor 6 days later with generalized weakness, fever, chills, and sweating. Vitals revealed temperature 38.3 °C, pulse rate of 115 bpm, blood pressure 163/98 mm Hg, respiratory rate 24 breaths per minute. Physical examination revealed an ill-appearing male and the rest of the examination was unremarkable.

The labs on the third admission are shown in Table 1. The kidney function labs continued to worsen despite intravenous fluids over the next 2 days, with blood urea nitrogen 23 mg/dL and creatinine 4.6 mg/dL. Ultrasound of the kidneys revealed right kidney measuring 9.3 cm in length, left kidney 9.7 cm in length, no stones, no masses, no hydronephrosis, and no cysts. The urine protein creatinine ratio was 0.8 mg/g and urine eosinophils were positive. Nephrology was consulted who recommended discontinuation of clozapine, initiation of oral steroids, and performing kidney biopsy.

Serologies for glomerulonephritis revealed normal complements, negative anti-nuclear antibody, negative anti-neutrophilic cytoplasmic antibody, negative anti-glomerular basement membrane antibody, negative hepatitis B and C virus studies, and negative human immunodeficiency virus serologies. Complete blood count did not reveal any eosinophilia. The kidney biopsy revealed 11 globally sclerotic glomeruli, no hypercellularity, no necrosis, and no crescents. Moderate interstitial fibrosis (50%) with associated tubular atrophy and moderate mononuclear interstitial inflammation with plasma cells and eosinophils (Figs. 1, 2). Moderate arteriosclerosis was present. No immune type or electron-dense deposits were identified on immunofluorescent and electron microscopy confirming the diagnosis of acute tubulointerstitial nephritis.

## Treatment

The serum creatinine plateaued around 4.0 - 4.1 mg/dL over the next few days. The patient was treated with 6 weeks tapering course of prednisone. The serum creatinine on discharge was 3.7 mg/dL. The serum creatinine returned to a baseline of 1.2 mg/dL at 2 months. The patient was treated with olanzapine, lorazepam, valproic acid, and paliperidone over the next year at assisted living without complete remission of symptoms.

## Follow-up and outcomes

The patient was readmitted to the inpatient psychiatric unit a year later with uncontrolled psychosis and worsening aggression. The patient had significant grandiose, religious, paranoid delusions. At that point, he was acting on his delusion which led to the physical injury of his partner, which precipitated inpatient psychiatric hospitalization. Considering treatment resistance and worsening aggression, the patient was rechallenged on treatment with clozapine 25 mg, and the dose was gradually up titrated to 75 mg daily over 3 days. The patient developed a fever with chills and rigors. Vitals revealed temperature 38.2 °C, pulse rate of 104 bpm, blood pressure 145/89 mm Hg, respiratory rate 20 breaths per minute. Physical examination was unremarkable. The labs revealed worsening serum creatinine from 1.31 mg/dL on admission to 1.91 mg/dL. Clozapine was stopped with the resolution of fever. Kidney function improved back to baseline in 2 weeks.

## Discussion

Clozapine, a tricyclic dibenzodiazepine is a second-generation atypical antipsychotic [2]. It exerts its anti-psychotic effects by antagonizing serotonin and dopamine receptors [2]. Clozapine is particularly used in treatment-resistant schizophrenia [3]. Treatment resistance is defined as failure to achieve remission despite using two or more antipsychotics [3]. Clozapine has fewer extrapyramidal side effects and less tardive dyskinesias compared to typical antipsychotics which makes it more appealing [2]. It is also effective in treating schizoaffective disorders and causes minimal changes in prolactin levels [2].

Despite the efficacy of clozapine, the use is limited by the side effect profile. The common side effects are fever, orthostasis, sialorrhea, oversedation, and more serious agranulocytosis [2]. Myocarditis, hepatitis, pancreatitis, vasculitis, pulmonary syndrome, and AKI due to interstitial nephritis are rarely encountered side effects [2]. Considering these potentially fatal side effects the use of clozapine is limited and should be offered only after two antipsychotics fail to achieve remission [3].

AIN classically presents as AKI most often induced by offending drugs. Less frequently AIN is secondary to infections, autoimmune disorders, and idiopathic causes [4]. The classic features of AIN include fever, rash, and eosinophilia, which may not be present in all cases. A high index of suspicion is needed in diagnosing AIN as a cause of AKI. AIN approxi-

**Table 1.** Laboratory Values During Hospitalizations

Parameters	On presentation	Reference range
The first admission labs		
Sodium (mmol/L)	141	135 - 145
Potassium (mmol/L)	4.0	3.5 - 5.1
Chloride (mmol/L)	108	98 - 106
CO <sub>2</sub> (mmol/L)	27	23 - 29
Anion gap (mmol/L)	10	8 - 14
Blood urea nitrogen (BUN) (mg/dL)	9	8 - 24
Creatinine (Cr) (mg/dL)	1.2	0.7 - 1.3
Glomerular filtration rate (mL/min)	60	> 90
White blood cells ( $\times 10^3/\text{mm}^3$ )	6.5	4 - 10
Hemoglobin (g/dL)	15.6	14 - 16
Platelets ( $\times 10^3/\text{mm}^3$ )	152	150 - 450
The second admission labs		
Sodium (mmol/L)	137	
Potassium (mmol/L)	3.5	
Chloride (mmol/L)	104	
CO <sub>2</sub> (mmol/L)	20	
Blood urea nitrogen (BUN) (mg/dL)	12	
Creatinine (Cr) (mg/dL)	1.61	
Glomerular filtration rate (mL/min)	44	
White blood cells ( $\times 10^3/\text{mm}^3$ )	6.3	
Hemoglobin (g/dL)	14.3	
Platelets ( $\times 10^3/\text{mm}^3$ )	224	
Total creatinine phosphokinase (U/L)	32	35 - 232
Thyroid-stimulating hormone (mIU/mL)	0.9	0.5 - 4.5
Serum lithium level (mmol/L)	0.9	0.5 - 1.5
Urine analysis		
Specific gravity	1.010	
pH	6.0	
Protein	None	
Glucose	None	
Blood	1+	
Nitrite	Negative	
Leucocyte esterase	Negative	
White blood cells	5/HPF	
Red blood cells	14/HPF	
The third admission labs		
Sodium (mmol/L)	135	
Potassium (mmol/L)	4.8	
Chloride (mmol/L)	102	
CO <sub>2</sub> (mmol/L)	20	
Blood urea nitrogen (BUN) (mg/dL)	19	
Creatinine (Cr) (mg/dL)	2.1	

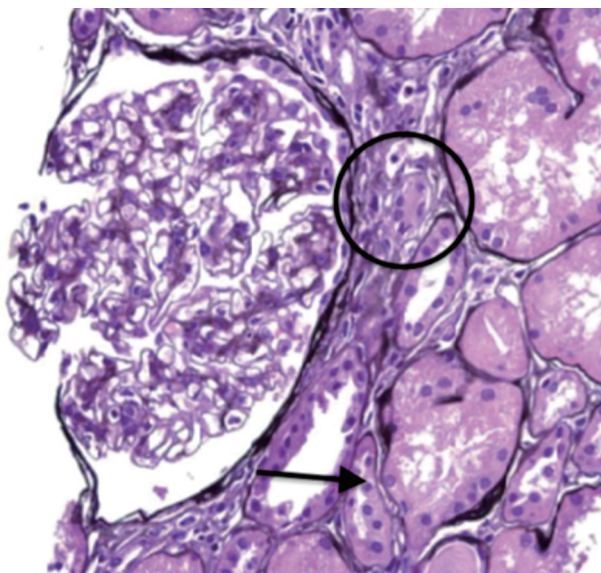
**Table 1.** Laboratory Values During Hospitalizations - (continued)

Parameters	On presentation	Reference range
Glomerular filtration rate (mL/min)	33	
White blood cells ( $\times 10^3/\text{mm}^3$ )	4.7	
Hemoglobin (g/dL)	11.7	
Platelets ( $\times 10^3/\text{mm}^3$ )	144	
Urine analysis		
Specific gravity	1.026	
pH	5.0	
Protein	2+	
Glucose	None	
Blood	1+	
Nitrite	Negative	
Leucocyte esterase	Negative	
White blood cells	21/HPF	
Red blood cells	8/HPF	

HPF: high power field.

mates 15-20% of AKI cases and contributes to 2.8% diagnosis of all the kidney biopsies [4]. The diagnosis is based on the clinical course and investigations. Particular attention should be paid to the history of infections, autoimmune diseases, and drug exposure history should be thoroughly sought. The offending agents should be promptly identified and stopped. The common drug classes which are known to cause AIN are antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). Tubular inflammation with cellular infiltrates and interstitial edema is the distinctive feature noted on the kidney biopsy and establishes the diagnosis.

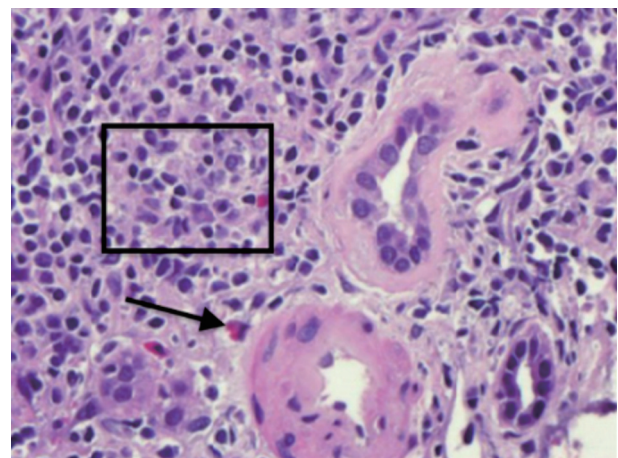
New onset proteinuria, hematuria, and AKI after initiat-



**Figure 1.** Periodic acid-Schiff staining displaying moderate mononuclear inflammation (circle) with associated tubular atrophy (arrow).

ing treatment with clozapine and improvement in the kidney function parameters after cessation of treatment establish the casual relationship. To the best of our knowledge, clozapine-induced AIN has been reported only 16 times in the literature review [5-20]. The clinical characteristics, investigations, kidney injury outcomes have been summarized in Tables 2 and 3.

AIN caused by clozapine is a drug hypersensitivity reaction, and rapid onset of AKI after rechallenging with clozapine supports that immunological memory plays a role in the pathogenesis [6]. Antigen reactive T cells play a fundamental role in dysregulating immunological response and may be contributing to AIN as supported by human and animal studies [4]. Foreign antigens are implicated in causing idiosyncratic hypersensitivity reactions. In drug-induced AIN, the idiosyncratic nature is distinctly indicated by the occurrence of reac-



**Figure 2.** Hematoxylin and eosin staining demonstrating moderate mononuclear interstitial inflammation (square) with plasma cells and eosinophil (arrow).

**Table 2.** Clinical Characteristics of AIN From Clozapine

Author	Age/ gender	Other antipsychotics	Antibi- otic use	Symp- tom onset	Fever	CRP	Symptoms sub- sided after stop- ping clozapine	Clozapine dose	Eosinophilia
Bassetti et al, 2021 [5]	54/F	Lurasidone, quetiapine	Yes	2 days	Yes	Not mentioned	Yes	50 mg daily	Not available
McLoughlin et al, 2019 [6]	56/F	Multiple typical and atypical antipsychotics	Yes	7 days	Yes	Elevated	Yes	275 mg daily	Present
Davis et al, 2019 [7]	59/M	Lithium, fluoxetine, fluphenazine, quetiapine, amantadine, depakote	No	21 days	No	Not mentioned	Yes	62.5 mg daily	Present
Caetano et al, 2016 [8]	25/M	Multiple but names not mentioned	No	20 days	Not mentioned	Elevated	Yes	300 mg daily	Not available
Chan et al, 2015 [9]	29/F	Quetiapine, sodium valproate	Yes	7 days	Yes	Not mentioned	Yes	700 mg daily	Not available
Parekh et al, 2014 [10]	54/M	Valproate	Yes	14 days	Yes	Elevated	Yes	100 mg daily	Not available
An et al, 2013 [11]	38/M	Lithium, valproate, risperidone	No	14 days	Yes	Elevated	Yes	200 mg daily	Not elevated
Mohan et al, 2013 [12]	53/F	Valproate	Yes	12 days	Yes	Not mentioned	Yes	200 mg daily	Present
Kanofsky et al, 2011 [13]	28/M	Lithium, valproate, haloperidol, perphenazine, benzotropine	Yes	12 days	Yes	Not mentioned	Yes	125 mg daily	Present
Hunter et al, 2009 [14]	57/F	Lithium, valproate, olanzapine, levomepromazine, haloperidol	Yes	2 days	Yes	Elevated	Yes	12.5 BID (rechallenge)	Not mentioned
Siddique et al, 2008 [15]	26/M	Lithium, valproic acid, risperidone, clonazepam	No	14 days	Yes	Not mentioned	Yes	125 mg daily	Present
Au et al, 2004 [16]	33/M	Valproate, gabapentin, risperidone	Yes	2 weeks	Yes	Not mentioned	Yes	100 mg daily	Present
Estebanez et al, 2002 [17]	69/M	Valproate	No	3 months	Unable to obtain	Unable to obtain	Yes	Unable to obtain	Unable to obtain
Fraser et al, 2000 [18]	49/M	Flupentixol, thioridazine, mianserin	Yes	35 days	Yes	Not mentioned	Yes	200 mg daily	Not present
Southall et al, 2000 [19]	24/F	Not mentioned	No	8 days	Yes	Elevated	Yes	300 mg daily	Present
Elias et al, 1999 [20]	38/F	Lithium, trifluoperazine, fluphenazine, venlafaxine	No	11 days	No	Not mentioned	Yes	125 mg BID	Not mentioned

AIN: acute interstitial nephritis; CRP: C-reactive protein; BID: twice a day; F: female; M: male.

**Table 3.** Kidney Function Parameters and Management of AIN From Clozapine

Author	Onset of renal failure	Urine eosinophils	Hematuria	Proteinuria	Renal imaging	Renal biopsy	Steroids	Dialysis needs	Residual dysfunction
Bassetti et al, 2021 [5]	18 days	Not available	Not available	Not available	Normal size and morphology	Not done	Yes	No	None
McLoughlin et al, 2019 [6]	Not mentioned in initial exposure, 2 days after rechallenge	Not available	Present	Not available	Both kidney 13.3 cm and mild prominences of both pelvises	Acute interstitial nephritis with 90% plasma cells	Yes	No	Yes
Davis et al, 2019 [7]	21 days	Not available	Not available	Present	Not mentioned	Not done	Not used	No	Yes
Caetano et al, 2016 [8]	24 days	Not available	Not available	Not available	Normal kidneys	Not done	No mention	No	No
Chan et al, 2015 [9]	7 days	Present	Present	Present	Normal sized kidneys	Tubulointerstitial nephritis, eosinophil rich infiltrates with occasional granulomas	No	No	No
Parekh et al, 2014 [10]	6 weeks	Not available	Present	Present	Bilaterally enlarged kidney and increased cortical echogenicity	Tubulointerstitial nephritis	Yes	No	No
An et al, 2013 [11]	19 days	Not available	Present	Present	CT diffuse swelling of both kidneys	Not done	No	Yes	No
Mohan et al, 2013 [12]	3 months	Not available	Not available	Present	Not available	AIN with 50% interstitial scarring	Yes	No	Yes
Kanofsky et al, 2011 [13]	13 days	Not performed	Not available	Present	Not available	Not done	Yes	No	No
Hunter et al, 2009 [14]	1 month in initial exposure, 2 days after rechallenge	Not mentioned	Yes	Yes	Not available	Not done	No	No	No
Siddique et al, 2008 [15]	2 weeks	Present	Not mentioned	Yes	Not available	Not done	Yes	No	At discharge 1.36
Au et al, 2004 [16]	2 weeks	Not mentioned	Yes	Yes	USS bilateral echogenicity	Not done	No	No	At discharge 4.1
Estebanez et al, 2002 [17]	3 months	Unable to obtain	Unable to obtain	Yes	Unable to obtain	Acute interstitial nephritis	Yes	No	Unable to obtain
Fraser et al, 2000 [18]	42 days	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Florid interstitial nephritis	Yes	Yes	No
Southall et al, 2000 [19]	8 days	Not mentioned	Yes	Yes	Not mentioned	Not done	No	No	No
Elias et al, 1999 [20]	11 days	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Mononuclear cell interstitial infiltrate, frequent eosinophils, prominent granulomatous component	No	Yes	No

AIN: acute interstitial nephritis; CT: computed tomography; USS: ultrasound scan.

tion in a minority of individuals, non-dose relation, systemic hypersensitivity presentation, and recurrence with re-exposure [4]. The simultaneous incidence of interstitial nephritis and cardiomyopathy and the presence of eosinophils support the possibility of immunoglobulin (Ig)E-mediated hypersensitivity reaction [15].

Elevated plasma levels of clozapine have been reported in the literature before once in clozapine-induced AIN, once in clozapine-induced pancreatitis, and twice in clozapine-induced hepatitis [6, 21]. The dosing of clozapine was around 300 mg in all the cases reported with elevated plasma levels [6]. Multitude factors play a role in the elevation of the plasma levels of clozapine including elevation of alpha1 acid glycoprotein which is an acute-phase protein and most of the clozapine bind to it [6]. Downregulation of the cytochrome P450 system by cytokines may also play a role [6]. Plasma clozapine level of 250 - 350 ng/mL is a reasonable target for a patient with schizophrenia. For those who have refractory symptoms, it is reasonable to target clozapine levels higher than 350 ng/mL despite limited evidence [22].

The occurrence of AIN with clozapine in the cases reported was approximately within 2 weeks in a majority but was delayed up to 1 - 3 months in a few cases as summarized in Tables 2 and 3. Kidney biopsy was done in seven cases which confirmed the diagnosis [6, 9, 10, 12, 17, 18, 20]. Clozapine rechallenge was done in three cases [5, 6, 14], which resulted in the occurrence of AKI within a few days or with few doses. The dosage of clozapine ranged from 25 mg to 700 mg in the cases where AKI occurred [6]. Proteinuria quantification was reported in only three cases and was in the sub nephrotic range [9, 10, 19]. A few patients had exposure to the antibiotics because of suspicion of infection, which may have perpetuated the AIN caused by clozapine, although there is no conclusive evidence [13]. Few patients never regained the baseline kidney function after developing AKI with clozapine [6, 7, 12, 15, 16]. About half of the patients in the cases reported were treated with steroids and only three patients needed dialysis which was outlined in Table 3. The factors to consider for favorable kidney health prognosis are baseline kidney function, kidney failure duration, kidney function trend after stopping the drug, and the length of exposure to the drug [6] (Table 3).

The clinical history of drug exposure, symptoms like fever and rash, and lab findings like eosinophilia, eosinophiluria, hematuria, proteinuria, sterile pyuria, and white blood cell (WBC) casts should raise the suspicion of AIN. Stopping the offending drug and resolution of clinical findings supports the diagnosis. Kidney biopsy is the gold standard test in establishing the diagnosis of interstitial nephritis, which is not done in all cases. Biopsy revealing the presence of eosinophils should point towards drug-induced AIN, while infection reveals the presence of neutrophils [9].

The mainstay in the treatment of interstitial nephritis is to stop the offending drug. Corticosteroids are used to hasten the recovery and prevent progression to chronic kidney disease (CKD). The electrolytes, acid-base status, and fluid balance should be carefully monitored, and provision of renal replacement therapy is warranted when needed. The patients should be followed by the nephrologist for any evidence of residual CKD and managed appropriately.

The Naranjo score is used to identify AIN as a possibility of drug reaction [23]. The causative drug is identified by the highest score accumulated. The Naranjo score calculated in our patient suggested that the interstitial nephritis is most likely caused by clozapine.

Lastly, we want to emphasize that although we did kidney biopsy in our case, biopsy is not always necessary to confirm AIN if the helpful positive findings like urine eosinophilia or exposure to known offending drugs are present in history and physical examination. However, as clozapine is very seldom known to cause AIN and it was the only lifesaving drug in this case of resistant psychosis, kidney biopsy was performed as a confirmative means before any decision was made to stop this drug.

### Learning points

This case report highlights the rare but serious side effect of clozapine causing AIN and the importance of prompt recognition and treatment. In addition to cell counts, it is pivotal to establish the baseline kidney function before treatment and close monitoring is warranted during treatment. Patients with drug reactions from the previous trial of clozapine should only be rechallenged if necessary and should be done with due caution. Early nephrology consultation should be obtained if there is evidence of kidney function impairment. Discontinuation of the offending agent and steroid therapy can reduce further kidney injury and can be lifesaving.

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### Financial Disclosure

None to disclose.

### Conflict of Interest

The authors have no conflict of interest to declare.

### Informed Consent

The patient consented for publication of this study.

### Author Contributions

Each author has been individually involved in and has made substantial contributions to conceptions and designs, acquisition of data, analysis, interpretation of data, drafting, and editing the manuscript. Praveena Vantipalli contributed to the acquisition of data, drafting, and editing of the manuscript.

Sasmit Roy contributed to the designs, analysis, interpretation of data, and editing of the manuscript and with final submission. Narayana M. Koduri contributed to the designs, interpretation of data, drafting, and editing of the manuscript. Venu Madhav Konala contributed to the drafting and interpretation of data. Amarinder Singh Garcha contributed to the drafting and editing of the manuscript. Srikanth Kunaparaju contributed to the drafting and editing of the manuscript. Raul Ayala contributed to the designs, analysis, and editing of the manuscript. Samanvitha Sai Yarram contributed to the analysis and editing of the manuscript. Sreedhar Adapa contributed to the designs, acquisition of data, analysis, interpretation of data, drafting, and editing of the manuscript.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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