CASE REPORT

Clozapine induced tubulointerstitial nephritis in a patient with paranoid schizophrenia

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Accepted 20 April 2014

SUMMARY

We describe the development of tubulointerstitial nephritis after starting clozapine therapy in a patient with treatment-resistant schizophrenia. A 54-year-old mixed-race patient with a longstanding history of paranoid schizophrenia was started on the antipsychotic clozapine. Two months after starting clozapine he developed fevers, cough and acute renal failure which initially responded to 7 days of prednisolone but recurred after completing the steroid course. Renal biopsy confirmed acute tubulointerstitial nephritis and he was started on a course of steroids with renal recovery in 72 h. Clozapine was later stopped. This case highlights a serious and potential life-threatening complication of an important antipsychotic used in treatment-resistant schizophrenia.

BACKGROUND

Clozapine has been widely used as a therapy for treatment-resistant schizophrenia with National Institute for Health and Clinical Excellence (NICE) guidelines stating that clozapine should be offered if no symptomatic relief is achieved after trying two different antipsychotics.¹ The risk of agranulocytosis is well recognised with regular full blood counts. However, the rare and potentially life-threatening complication of interstitial nephritis is not well known or documented.

This case describes the development of acute tubulointerstitial nephritis associated with clozapine therapy, which we hope will increase awareness among psychiatrists and physicians, to help with early recognition of this serious complication.

CASE PRESENTATION

A 54-year-old mixed-race man was admitted in May 2012 from the inpatient psychiatric unit with worsening renal failure and rising inflammatory markers, following two previous admissions over the past 3 months. He has a medical history of paranoid schizophrenia diagnosed in 2002 for which he is managed in an inpatient psychiatric ward following poor treatment outcomes in the community. He also has a history of chronic obstructive airways disease and normocytic anaemia.

Various antipsychotics including risperidone and aripiprazole were previously tried without symptomatic improvement; he was therefore started on sodium valproate (February 2011) and clozapine 100 mg (15 February 2012) by his psychiatric team.

First admission—3 March 2012

Two weeks following the start of clozapine therapy he was admitted to hospital with a fever, sputum production, chest pain and shortness of breath. Blood tests showed a white cell count (WCC) of $9.8 \times 10^9/L$ ($4.5\text{--}11.0 \times 10^9/L$), C reactive protein (CRP) of 173 mg/L (0–8 mg/L) and creatinine of $88 \mu\text{mol/L}$ ($63\text{--}111 \mu\text{mol/L}$). He was treated for a lower respiratory tract infection with fluids and intravenous tazocin. CT of the chest demonstrated previous apical scarring and moderate centrilobular emphysema.

Second admission—16 April 2012

One month after being discharged he was readmitted with fatigue, anorexia, raised inflammatory markers and acute kidney injury. On this admission blood tests showed a WCC of $14.2 \times 10^9/L$ ($4.5\text{--}11.0 \times 10^9/L$), CRP of 211 mg/L (0–8 mg/L) and creatinine of $188 \mu\text{mol/L}$ ($63\text{--}111 \mu\text{mol/L}$). Chest radiograph showed left lower zone shadowing and he was treated with fluids and tazocin for presumed pneumonia. He was also started on a 7-day course of oral prednisolone for presumed exacerbation of his obstructive airways disease.

This admission—4 May 2012

Three weeks later the patient was readmitted with a normocytic anaemia, acute kidney injury and raised inflammatory markers. Blood tests showed a haemoglobin of 9.9 g/dL (13.0–17.5 g/dL), WCC of $12.5 \times 10^9/L$ ($4.5\text{--}11.0 \times 10^9/L$), creatinine of $310 \mu\text{mol/L}$ ($63\text{--}111 \mu\text{mol/L}$), urea of 15.8 mmol/L (3.2–7.4 mmol/L) and CRP of 157 mg/L (0–8 mg/L). He denied any symptoms on this admission and felt well. He was afebrile, normotensive, euvolaemic and passing normal volumes of urine on admission. His urinalysis showed a trace of blood, a protein level of 100 mg/dL and was nitrite positive and leucocyte negative.

Initial improvement with fluid resuscitation was achieved with reduction of creatinine to $169 \mu\text{mol/L}$ 5 days after admission. However, following this, creatinine and CRP remained static. Renal ultrasound showed bilaterally enlarged kidneys (right kidney 13 cm and left kidney 12.6 cm) and increased cortical echogenicity. Twenty-four hour urine collection showed elevated protein levels 1.3 g/day (0.01–0.14 g). Renal function and inflammatory markers continued to worsen with peak values showing creatinine $453 \mu\text{mol/L}$ ($63\text{--}111 \mu\text{mol/L}$) and CRP 261 mg/L (0–8 mg/L) with no focus of infection, therefore antibiotics were stopped. Blood tests sent for further investigation of renal impairment showed

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To cite: Parekh R, Fattah Z, Sahota D, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-203502

the patient was positive for an antinuclear antibody (shown to be a proliferating cell nuclear antigen—PCNA).

Review by the renal physicians suggested performing renal biopsy to further investigate renal function deterioration. The biopsy demonstrated tubulointerstitial nephritis (see figures 1A,B). He was started on oral prednisolone and his renal function and inflammatory markers dramatically improved within 1 week (see figure 2). This graph demonstrates the correlation between raised inflammatory markers and kidney injury, with the three separate admissions indicated. The dramatic improvement with steroid therapy can be seen.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of the aetiology of acute tubulointerstitial nephritis can be categorised into drug induced, immunological and infectious.

Given the lack of a source of infection and response to broad spectrum antibiotics, bacterial infection does not seem to fit as the aetiology in this case. Viral screen confirmed that there was no evidence of HIV, hepatitis B, C or cytomegalovirus infection.

Immunological causes of tubulointerstitial nephritis include Sjogren's syndrome, sarcoidosis and systemic lupus erythematosus (SLE). There are no sicca symptoms or signs suggesting either Sjogren's syndrome or sarcoidosis. An interesting aspect

of this case was the finding of positive autoantibody result (PCNA), which is shown to be highly specific for SLE.² Given this finding the consultant clinical pathologist examined the histology slides and found no features to suggest lupus nephritis. In addition, further immunological blood results showed no evidence of SLE. The complement component 3 (C3) level was 1.18 g/L (0.82–1.85 g/L), the complement component 4 (C4) level was 0.19 g/L (0.15–0.53 g/L), the anti-dsDNA screen test was negative and the following autoantibodies: anti-SSA-Ro, anti-SSA-La, anti-RNP, anti-SM, anti-Jo1 and anti-Scl-70 were all negative. There was also no evidence of neutropenia, lymphopenia, rashes, photosensitivity, arthritis, oral ulceration or serositis.

The remaining aetiology is drug-induced nephritis. There are over 100 drug causes of tubulointerstitial nephritis, with relevant drugs including sodium valproate and antibiotics (penicillin, quinolones, cephalosporins and β -lactam antibiotics have been shown to be causative).³ However, the timeline of onset of symptoms and order of drug administration shows that it is unlikely sodium valproate is implicated, as this was started over a year prior to this episode and he was stable until this episode. Tazocin had been used; however, this was used after the development of symptoms.

Therefore the diagnosis of clozapine-induced tubulointerstitial nephritis seems most likely; this has been reported in eight published cases (see below).

TREATMENT

Following renal biopsy the patient was started on a course of oral prednisolone 30 mg daily for 1 week and this was then titrated down by 5 mg every 3 days. Clozapine was eventually stopped.

OUTCOME AND FOLLOW-UP

He was followed up by the renal team in clinic and showed sustained normal renal function with steroid treatment.

The patient was also referred to the rheumatology department for further investigation for neuropsychiatric lupus. He is currently undergoing treatment with cyclophosphamide and prednisolone and is being followed up with the rheumatology and psychiatric teams.

DISCUSSION

There are eight published cases of clozapine-induced interstitial nephritis.^{4–11} The demographics of patients in these reports vary with three female and five male reports. The age of these patients varies from 24 to 69 years. Analysis of the cases demonstrates variability with onset of symptoms after starting clozapine therapy ranging from less than a day to 3 months. Common symptoms seen in the cases include fever (6/8), esophiniphilia (4/8) and proteinuria (6/8).

When comparing these reports to our case report, the symptoms of fever, raised WCC, raised inflammatory markers and proteinuria correspond well. The timing of onset does differ considerably with previous cases as there is a delay of 2 months from starting clozapine therapy to the onset of symptoms. The first admission does not appear to be related, considering the resolution of the inflammatory markers and acute kidney injury to normal levels with fluids and antibiotics.

Another interesting point in our case is the presence of the anti-PCNA antibody. PCNA is an intranuclear protein that plays a role in DNA repair and replication.² In a review of 7661 patients with positive antinuclear antibody (ANA), only 29 were positive for anti-PCNA (ie, 0.4% of ANA positive patients).

Figure 1 (A) *Renal biopsy*: Periodic Acid Schiff-stained section showing a heavy interstitial inflammatory infiltrate with many plasma cells. There is a normal glomerulus in the top left. The arrows show tubular profiles with the diagnostic lesion of tubulitis (ie, monocytes within the tubular epithelium) which suggests a diagnosis of acute tubulointerstitial nephritis. (B) *Renal biopsy*: H&E stain showing inflammation in the interstitium with plasma cells. The arrows indicate tubules with the diagnostic lesion of tubulitis (monocytes within the tubular epithelium) confirming a diagnosis of acute tubulointerstitial nephritis.

Scatter graph showing changes in creatinine and C-reactive protein over time

Figure 2 Scatter graph demonstrating the change in creatinine and C reactive protein through multiple admissions and steroid therapy. The dramatic improvement with the start of steroid therapy can be seen.

Of the 29 patients, only 2 had SLE nephritis diagnosed 4 and 5 years earlier; the remainder had a myriad of autoimmune conditions.¹² Additionally, to determine the prevalence of anti-PCNA antibody in a cohort of 275 patients who met the American College of Rheumatology criteria for the diagnosis of SLE, only 3 patients had anti-PCNA. One patient was positive at diagnosis, one became positive at the first relapse and the other had no nephritis.¹² This indicates that PCNA positivity seems to be highly associated with renal involvement. This led us to look closely for SLE changes in the renal histology for detecting SLE nephritis changes; however, no specific changes indicative of lupus nephritis were found and other immunological blood tests were unremarkable. Therefore the diagnosis of SLE remains very unlikely. He remains under close follow-up by the rheumatology and renal team.

Learning points

- ▶ When starting a patient on clozapine, it is important to consider the patient's risk of developing tubulointerstitial nephritis.
- ▶ Signs of developing tubulointerstitial nephritis include fevers, proteinuria and raised white cell counts.
- ▶ It is important to consider inflammatory as well as infective causes of raised inflammatory markers in patients.

Contributors All authors contributed towards design, drafting and final approval of the article.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 NICE. Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. *NICE* 2009;CG82.
- 2 Beyne-Rauzy O, Thebault S, Adoue D. Anti-PCNA antibodies: prevalence and predictive value. *Joint Bone Spine* 2005;72:432–5.
- 3 Rossert J. Drug-induced acute interstitial nephritis. *Kidney Int* 2001;60:804–17.
- 4 Southall KE, Fernando SN. A case of interstitial nephritis on clozapine. *Aust N Z J Psychiatry* 2001;34:697–8.
- 5 Elias J, Bannister KM, Clarkson AR, et al. Clozapine-induced acute interstitial nephritis. *Lancet* 1999;354:1180–1.
- 6 Hunter R, Gaughan T, Queirazza F, et al. Clozapine-induced interstitial nephritis—a rare but important complication: a case report. *J Med Case Rep* 2009;3:8574.
- 7 Au AF, Luthra V, Stern R. Clozapine-induced acute interstitial nephritis. *Am J Psychiatry* 2004;161:1501.
- 8 Estébanez C, Fernández MJR, Sánchez RH, et al. Nefritis intersticial aguda inducida por clozapina. *J Nephrol* 2002;22:277–81.
- 9 Fraser D, Jibani M. An unexpected and serious complication of treatment with the atypical antipsychotic drug clozapine. *Clin Nephrol* 2000;54:78–80.
- 10 Kanofsky JD, Woessner ME, Harris AZ, et al. A case of acute renal failure in a patient recently treated with clozapine and a review of previously reported cases. *Prim Care Companion CNS Disord* 2011;13.
- 11 Siddiqui BK, Asim S, Shamim A, et al. Simultaneous allergic interstitial nephritis and cardiomyopathy in a patient on clozapine. *Clin Kidney J* 2008;1:56.
- 12 Vermeersch P, Beeck KOD, Lauwerys BR, et al. Antinuclear antibodies directed against proliferating cell nuclear antigen are not specifically associated with systemic lupus erythematosus. *Ann Rheum Dis* 2009;68:1791–3.

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