

# Myocarditis in a Patient on Clozapine: What did it?

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## Abstract

We are presenting the case of a 37-year-old male with schizoaffective disorder who developed myocarditis within three weeks of starting on clozapine for his treatment-resistant psychosis. The patient also had a positive titer for Influenza A, which makes it a diagnostic dilemma regarding the cause of his myocarditis. It may be possible that the myocarditis was caused by the Influenza A virus or synergistically exacerbated the clozapine's propensity to cause it. Currently, there are no studies establishing the link between the two etiologies. As clozapine can be the only option for patients resistant to treatment of their psychiatric illness, and there being some evidence for successful rechallenge of clozapine, we consider that this patient could have benefited from a trial of a rechallenge; however, he was lost to follow-up.

**Key Words:** Clozapine, Myocarditis, Rechallenge, Influenza

## Introduction

Clozapine is an atypical antipsychotic with a well-known efficacy for the treatment of resistant psychosis. Clinicians are well aware of the drug's metabolic, hematologic and anticholinergic side effects. Less attention is given to clozapine's cardiac side effects such as myocarditis, despite a high associated mortality rate. The need to consider myocarditis as one of the causes of flu-like symptoms in patients taking clozapine should be well entrenched as early intervention might improve the prognosis of the patient significantly. Also, acute myocarditis is a well-known complication of a viral infection which accounts for significant morbidity and mortality.

## Case Presentation

Mr. M is a 37-year-old white male with a history of schizoaffective disorder, bipolar type who presented to the

hospital with paranoid delusions, disorganized behavior and racing thoughts after a period of noncompliance of medications for three months.

He had his onset of symptoms at the age of nineteen years and has been since seeking treatment. He was well controlled on his medications for a period of five years before this episode, which included olanzapine and valproic acid. The patient had a poor social support system, used to live alone and did not maintain much contact with the family members. He recently broke up with his girlfriend leading to the noncompliance of medications. He denied any current substance use.

Patient was initially started on his home medications including olanzapine and valproic acid. After a trial of more than two weeks with maximum doses of 30 mg/day and 1,250 mg/day, respectively, and the patient still being symptomatic (disorganized, showing limited insight to his condition and demonstrating paranoid ideations), he was switched to haloperidol and later to quetiapine. Again, there was no significant response after a trial of two weeks each with maximum doses of 10 mg/day and 600 mg/day, respectively. Valproic acid was continued throughout treatment as patient had a previous unknown allergic reaction to lithium.

Patient only had a partial improvement in his symptoms; therefore, clozapine was started and cross titrated with que-

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tiapine with the aim of targeting the remaining disorganization and paranoia. Dose was titrated starting initially from 50 mg daily to 200 mg daily in a week. Patient showed marked improvement in his symptoms and discharge planning was in process after his treatment optimization with respect to the clozapine.

### Course of Illness

After eighteen days of starting clozapine, patient had an episode of fever (101.5 F), shortness of breath, chest pain, and hypotension (90/50mm Hg) and was rushed to the ER. In the ER, his troponins were significantly elevated at 7.4 (normal range 0–0.06 ng/mL). EKG had new ST wave changes. This was preceded by the patient having nonspecific malaise, nausea and weakness for a couple of days. Chest CT and CXR were unremarkable. The patient was brought to the cardiac cath lab and, subsequently, patient was catheterized, which revealed normal coronary arteries along with hypokinesis of the inferior wall motion. His ejection fraction was 45%. Clozapine was discontinued immediately due to a concern that it caused the myocarditis. Patient was subsequently transferred to the ICU, was stabilized on IV fluids, transient use of beta blocker and a calcium channel blocker.

After the patient was stabilized (about five days) and his vitals were within normal limits, he was transferred back to the psychiatry unit. Upon discharge, the patient also had an influenza A titer of 1:32 (<1:8 no antibody detected), which indicated a recent infection, broadening the differential to a viral myocarditis. As per infectious disease recommendations, the patient was put on oseltamivir 75 mg BID for five days. When he returned to the psychiatric unit, clozapine was listed as an allergy in his chart. He was subsequently put back on olanzapine and valproic acid, with reduction in paranoia and disorganized behavior over time until he was suitable for discharge. At the time of discharge, he was behaviorally stable but still displayed some paranoia and was not at his baseline. He was given appropriate outpatient referrals; however, he failed to follow through and was lost to follow-up.

### Discussion

Myocarditis developing in a patient with clozapine is a rare phenomenon with the occurrence of .015–0.188% (1, 2). There is a very high mortality associated with this condition. The symptoms of myocarditis are fever, tachycardia, chest pain, elevated cardiac enzymes, eosinophilia and EKG changes (3).

There is still no consensus regarding the pathophysiology of clozapine-induced myocarditis. As per Kilian et al., the time to onset of symptoms and the presence of myocardial eosinophilic infiltrates in several cases are consistent with drug-induced, acute hypersensitivity (type I, IgE-mediated)

myocarditis (2). Devarjan et al. reported that such patients may lack CYP 450 enzymes that are responsible for clozapine metabolism, thereby resulting in extreme clozapine concentrations leading to potential cardiotoxicity (4). As per Hagg et al., clozapine-related hypereosinophilic syndrome may cause direct cardiotoxic effects of eosinophils through the blockade of cholinergic M2 receptor (6). A study by Wang et al. postulated a hypercatecholaminergic state induced by clozapine could explain the occurrence of myocarditis in some patients (7). It could very well be a combination of these possible mechanisms which resulted in clozapine-induced myocarditis.

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Influenza A is a well-known cause of acute myocarditis. The clinical severity ranges from asymptomatic to fulminant varieties. The frequency of myocardial involvement in influenza infection is variable, with rates of up to 10% having been reported in the literature although this is dependent on the methods used to detect myocardial involvement (8). It is hypothesized that the pro-inflammatory state induced by the viral infection leads to myocarditis (9).

Brain and peripheral catecholamines, including norepinephrine and epinephrine, have been shown to be elevated by clozapine, and persist throughout clozapine treatment in animals and humans (10, 11). It has also been shown by Wang et al. that epinephrine exacerbated viral myocarditis in a murine model (12). Thus, from the evidence available so far, it is therefore likely that both clozapine and influenza both may synergistically increase the risk of myocarditis via a hypercatecholaminergic state, as it may have happened in our case.

As per the current recommendations, once clozapine-related myocarditis has been diagnosed, it is mandatory to immediately stop clozapine treatment. It has shown that early cessation of clozapine treatment may improve the clinical outcomes (1, 2). There is a proposed monitoring protocol which recommends cessation of clozapine if troponin is more than twice the upper limit of normal or C-reactive protein is over 100 mg/L. Combining these two parameters has an estimated sensitivity for symptomatic clozapine-induced myocarditis of 100% (13).

However, some experts recommend rechallenge in patients who have had substantial benefits from clozapine and

who have limited subsequent response from any other available antipsychotics. From the largest retrospective case series of patients who were rechallenged with clozapine following myocarditis, delayed rechallenge with gradual up titration of clozapine dose appeared to reduce the risk of cardiomyotoxicity (14).

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Our patient was treated with a full course of oseltamavir for influenza, and he still continued to have residual psychiatric symptoms at the time of discharge. Having had a prior good response to clozapine, it could have been a reasonable choice to rechallenge this patient with clozapine using the available recommendations with the collaboration of cardiologist and primary care provider, weighting the risks and benefits of myocarditis versus improved functioning. Also, considering the nuances of rechallenge already in a patient with documented myocarditis, it is imperative to set up adequate and stable psychosocial supports in the community. However, this patient did not follow up with his outpatient appointments and was lost to follow-up. More information is needed regarding the risk-benefit analysis of restarting clozapine after a concern for myocarditis. Further, the role of screening for influenza in clozapine-treated patients who develop myocarditis could be considered, particularly in pa-

tients with a documented recent flu-like illness as they may represent a subset of patients who may tolerate rechallenge better after the viral infection has resolved.

## References

- Merrill DB, Ahmari SE, Bradford JM, Lieberman JA. Myocarditis during clozapine treatment. *Am J Psychiatry* 2006;163(2):204-208.
- Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999;354(9193):1841-1845.
- Wooltorton E. Antipsychotic clozapine (Clozaril): myocarditis and cardiovascular toxicity. *CMAJ* 2002;166(9):1185-1186.
- Devarajan S, Kutcher SP, Dursun SM. Clozapine and sudden death. *Lancet* 2000;355(9206):841.
- De Berardis D, Serroni N, Campanella D, Olivieri L, Ferri F, Carano A, et al. Update on the adverse effects of clozapine: focus on myocarditis. *Curr Drug Saf* 2012;7(1):55-62.
- Hägg S, Spigset O, Bate A, Soderstrom TG. Myocarditis related to clozapine treatment. *J Clin Psychopharmacol* 2001;21(4):382-388.
- Wang JF, Min JY, Hampton TG, Amende I, Yan X, Malek S, et al. Clozapine-induced myocarditis: role of catecholamines in a murine model. *Eur J Pharmacology* 2008;592(1-3):123-127.
- Mamas MA, Fraser D, Neyses L. Cardiovascular manifestations associated with influenza virus infection. *Int J Cardiol* 2008;130(3):304-309.
- Ukimura A, Satomi H, Ooi Y, Kanzaki Y. Myocarditis associated with influenza A H1N1pdm2009. *Influenza Res Treat* 2012;2012:351979.
- Elman I, Goldstein DS, Eisenhofer G, Folio J, Malhotra AK, Adler CM, et al. Mechanism of peripheral noradrenergic stimulation by clozapine. *Neuropsychopharmacology* 1999;20(1):29-34.
- Green AI, Alam MY, Sobieraj JT, Pappalardo KM, Waternaux C, Salzman C, et al. Clozapine response and plasma catecholamines and their metabolites. *Psychiatry Res* 1993;46(2):139-149.
- Wang JE, Meissner A, Malek S, Chen Y, Ke Q, Zhang J, et al. Propranolol ameliorates and epinephrine exacerbates progression of acute and chronic viral myocarditis. *Am J Physiol Heart Circ Physiol* 2005;289(4):H1577-H1583.
- Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust N Z J Psychiatry* 2011;45(6):458-465.
- Ronaldson KJ, Fitzgerald PB, Taylor AJ, McNeil JJ. Observations from 8 cases of clozapine rechallenge after development of myocarditis. *J Clin Psychiatry* 2012;73(2):252-254.