

CLINICAL VIGNETTE

Clozapine-Induced Myocarditis

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Case Report

A 26-year-old African American man with a 10 year history of psychotic mood disorders and who was experiencing worsening paranoia, disorganization, and odd behaviour over the past several months was brought into the emergency department by his family. The patient was evaluated by a Psychiatrist in the ED, placed on a “medical hold” for grave disability, and admitted to the psychiatric ward for further treatment.

The patient’s psychiatric history began in 2005 when he was first diagnosed with schizoaffective disorder at age 17, after experiencing paranoid delusions and auditory hallucinations. He received care at the Adolescent Psychosis Clinic, whereby his symptoms were well-managed with risperidone, trazodone, and quetiapine. The patient was doing well up until 2011 when he decided to discontinue risperidone due to the undesired side effect and feeling “so drugged up.” His symptoms relapsed with more erratic and paranoid behavior. He also lost his job, severed many of his relationships, and became more isolated. The patient also failed to follow up with his Psychiatrist.

He did not have any other co-morbid medical conditions. Family history was significant for a mother with bipolar disorder. Social history is remarkable for distant history of marijuana use. He had no known drug allergies.

During hospitalization, risperidone was restarted for psychosis. There was little improvement, so risperidone was changed to lurasidone, which also failed to control his symptoms.

Given the refractory nature of his schizoaffective disorder, clozapine was started at 25 mg nightly with up-titrate per standard protocol.

The patient showed initial improvement with clozapine. He had less paranoia, improved insight, and better thought organization. The medication was increased to 250 mg daily to achieve optimal effect. However on the 12th day of clozapine use, the patient complained of flu-like symptoms, including fevers, chills, fatigue, and myalgias.

On day 15th of treatment, the patient began experiencing substernal chest pain with a low blood pressure of 75/37. This prompted an urgent evaluation including an EKG that demonstrated ST elevations in leads II, AVF, AVL, V4-6 with PR depression in II (Figure 1) and an elevated serum Troponin to 5.8 ng/ml (Reference range: <0.1ng/ml). The patient was transferred to the Coronary Care Unit (CCU) for further management. Other laboratory studies included

elevated CRP and ESR at 3.5 mg/dL and 28 mm/hr, respectively.

The patient was placed on continuous cardiac monitoring in the CCU. Clozapine was immediately discontinued given suspicion of clozapine induced myocarditis. Colchicine 0.6mg BID and ibuprofen 600mg TID were started (for 3 months and 10 days, respectively).

Serum Troponin peaked at 15.2 ng/ml and eventually normalized after discontinuing clozapine and starting ibuprofen and colchicine. The chest pain also resolved and the EKG normalized. Echocardiogram demonstrated preserved cardiac function with an ejection fraction of 55-60% without any wall motion abnormality.

Discussion

Clozapine is an atypical, dibenzodiazepine antipsychotic with strong dopaminergic and serotonergic activity. It is primarily used in patients with treatment-resistant schizophrenia or in those who cannot tolerate other antipsychotics.¹

Clozapine was originally introduced in Europe in 1975 as one of the first atypical antipsychotics but was withdrawn after reports of fatal infections secondary to agranulocytosis.^{1,2}

Clozapine was reapproved for use in 1989 in the United States and in 1990 in the United Kingdom after it was shown to offer clinical benefits in treatment resistant schizophrenia. However, use of the medication required hematological monitoring with a new black box warning of agranulocytosis¹.

In 2002, Myocarditis was added to clozapine’s black box warnings when post-marketing surveillance data revealed an increased risk of myocarditis.

Data from FDA’s MedWatch Reporting System revealed 30 cases of myocarditis with 17 fatalities among 205,493 patients treated in the United States (August 2001), 7 cases with 1 fatality in 15,600 patients in Canada (April 2001), and 30 cases with 8 fatalities in 24,108 patients in the United Kingdom (August 2001). These reports correspond to an incidence rate of 5.0, 16.3, 43.2, and 96.6 cases/100,000 patient years, respectively.²

Based on a retrospective review of 116 suspected clozapine-induced myocarditis in Australia, the typical patient was 30 years old (younger than the average age of 37 in unaffected

patients) and developed myocarditis within a median of 16 days of medication commencement.³ More than 90% of patients were taking clozapine within the dose range of 100mg/day to 450mg/day (i.e., during the up-titration stage).

Another retrospective review from the United States demonstrated similar epidemiological results but also noted that those who survived myocarditis tended to have been treated for a shorter time (median 2 weeks vs. 4 weeks) and took a lower daily dose (median 225 mg vs. 450 mg).⁴

More common but less serious cardiac side effects of clozapine include orthostatic hypotension and tachycardia. Orthostatic hypotension affects about 9% of patients.⁵ It is more likely to occur during the initial up-titration and rapid dose escalation, and in rare cases (1/3000), patients may progress to circulatory collapse.

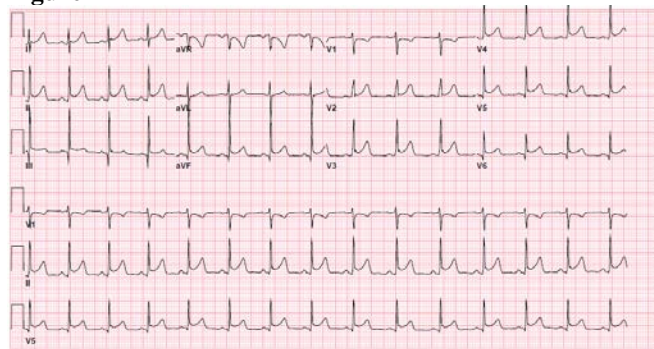
Tachycardia affects about 25% of patients who have 10-15 beats per minute rise in their heart rate.⁵ Tachycardia does not appear to be a reflex response to orthostatic hypotension as tachycardia was present regardless of patient position. Though benign in most patients, tachycardia and orthostatic hypotension may be problematic in those with pre-existing cardiac conditions.

Myocarditis, however, can affect those who are otherwise healthy with no pre-existing cardiovascular risk factors. Myocarditis should be suspected when a patient develops chest pain or dyspnea. Often it is preceded by a prodrome of flu-like symptoms, such as fever, myalgias, or dizziness, though many of these symptoms are non-specific and may be related to the drug's α -adrenergic properties.²⁻⁷

Once myocarditis is suspected, clozapine therapy should be immediately discontinued and never restarted. Patient should also be transferred to a cardiac unit for further management.

Because clozapine's damage to the heart appears to be an immune-mediated reaction, possible therapies include NSAIDs, colchicine, and corticosteroids. Despite these interventions, clozapine-induced myocarditis is fatal in many cases, and as such, early recognition of myocarditis in patients who develop chest pain is vital.

Figure 1



REFERENCES

1. **Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA.** Clozapine-induced agranulocytosis. Incidence and risk factors in the

United States. *N Engl J Med.* 1993 Jul 15;329(3):162-7. PubMed PMID: 8515788.

2. **Kakar P, Millar-Craig M, Kamaruddin H, Burn S, Loganathan S.** Clozapine induced myocarditis: a rare but fatal complication. *Int J Cardiol.* 2006 Sep 20;112(2):e5-6. Epub 2006 Jun 30. PubMed PMID: 16808983.
3. **Haas SJ, Hill R, Krum H, Liew D, Tonkin A, Demos L, Stephan K, McNeil J.** Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. *Drug Saf.* 2007;30(1):47-57. Review. PubMed PMID: 17194170.
4. **La Grenade L, Graham D, Trontell A.** Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N Engl J Med.* 2001 Jul 19;345(3):224-5. PubMed PMID: 11463031.
5. **Kilian JG, Kerr K, Lawrence C, Celermajor DS.** Myocarditis and cardiomyopathy associated with clozapine. *Lancet.* 1999 Nov 27;354(9193):1841-5. PubMed PMID: 10584719.
6. **Hägg S, Spigset O, Bate A, Soderström TG.** Myocarditis related to clozapine treatment. *J Clin Psychopharmacol.* 2001 Aug;21(4):382-8. PubMed PMID: 11476122.
7. **Ronaldson KJ, Taylor AJ, Fitzgerald PB, Topliss DJ, Elsik M, McNeil JJ.** Diagnostic characteristics of clozapine-induced myocarditis identified by an analysis of 38 cases and 47 controls. *J Clin Psychiatry.* 2010 Aug;71(8):976-81. doi: 10.4088/JCP.09m05024yel. Epub 2010 Mar 9. PubMed PMID: 20361910.

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