Case Report

Clozapine Induced Myocarditis: a case report

Javed Ather Siddiqui[1], Shazia Farheen Qureshi[1], Ali Mahmoud Eldaous1

[1]Psychiatrist, Department of Psychiatry, Mental Health Hospital, Taif, Saudi Arabia.
Corresponding author: Javed Ather Siddiqui
Email – javedsiddiqui2000@gmail.com

ABSTRACT

Clozapine is commonly used in resistant schizophrenia, but its use has been limited because of side effects. Myocarditis is one of the rare and potentially fatal side effects that can occur at any time after initiation of treatment but typically occurs within 2 to 3 weeks after initiation treatment with clozapine. We report the case of a 28-year-old patient who developed myocarditis after initiation treatment with clozapine, and a successful re-challenge of starting Clozapine. The physician should be cautious during the initiation of rapid clozapine titration early in treatment and follow the guidelines of close monitoring with laboratory investigation. This allows the early detection of myocarditis and reduces the risk of fatal mortality.

Keywords: Clozapine, myocarditis, schizophrenia

(Paper received – 26th January 2023, Peer review completed – 18th February 2023)
(Accepted – 25th February 2023)

INTRODUCTION

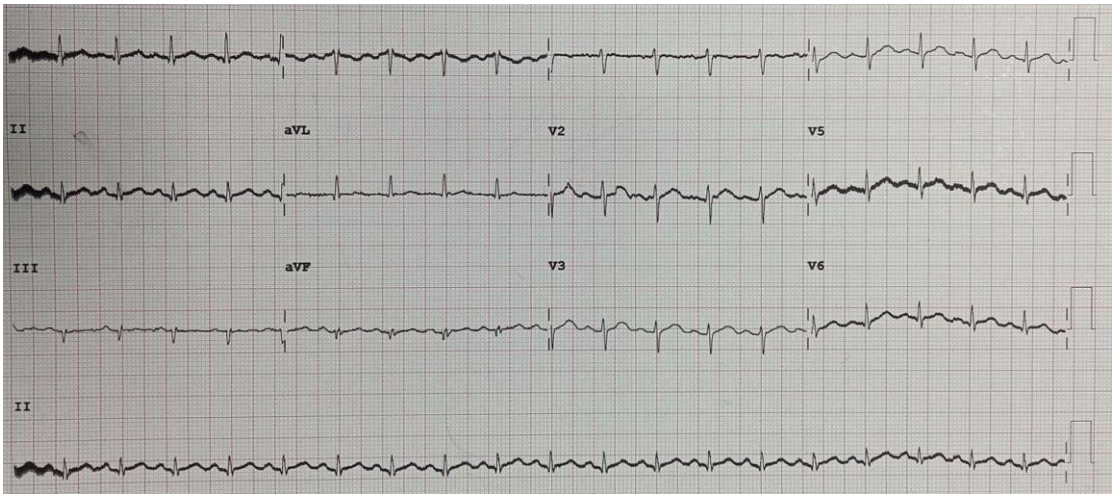
Clozapine is an atypical antipsychotic dibenzo-diazepine derivative, commonly used in patients with treatment-resistant schizophrenia. Benefits of clozapine are that it carries a low risk of extrapyramidal side effects and that it reduces both positive and negative symptoms. It also significantly reduces aggression and risk of suicide [1-2]. Due to its fatal side effect profile, its use is limited, and it is essential to monitor it after starting the medication [3]. These rare, potentially fatal side effects, such as reversible neutropenia, can lead to agranulocytosis, and myocarditis [4]. Other side effects of clozapine include hypersalivation, constipation, urinary incontinence, postural hypotension, nausea, and tachycardia. Myocarditis is a rare, poorly understood, potentially life-threatening condition characterized by inflammation of cardiac muscle, and associated with 5 to 20 percent of all cases of sudden cardiac death in young adults [5]. Causes of myocarditis may non-infectious, such as toxins like carbon monoxide, arsenic, ethanol, hypersensitivity to drugs, or pre-existing autoimmune disease. In the literature, clozapine-induced myocarditis is observed in 3 percent of patients receiving clozapine [6].

CASE REPORT

A 28-year-old, Saudi male patient was admitted to our hospital due to his disturbed behaviour such as anger outbursts, suspiciousness, hearing voices of someone talking to him for more than 6 months with social and occupational dysfunction due to psychotic symptoms. He was diagnosed with a case of schizophrenia. During his hospital stay, he was prescribed several antipsychotics, including haloperidol 15 mg per day for the first three months, olanzapine 20 mg for another three months, and amisulpride 600 mg per day for three more months, without significant improvement in his symptoms. There was no history of substance, or illicit drug use. Because he did not respond to other antipsychotics, he was switched to clozapine. There is no history of autoimmune disease. No recent episode of acute respiratory illness was noted. The viral antibody titer test was normal, so viral myocarditis was ruled out. Work-up for starting clozapine was done; all routine investigations such as complete blood cell count, liver and kidney function tests, serum electrolytes and lipid

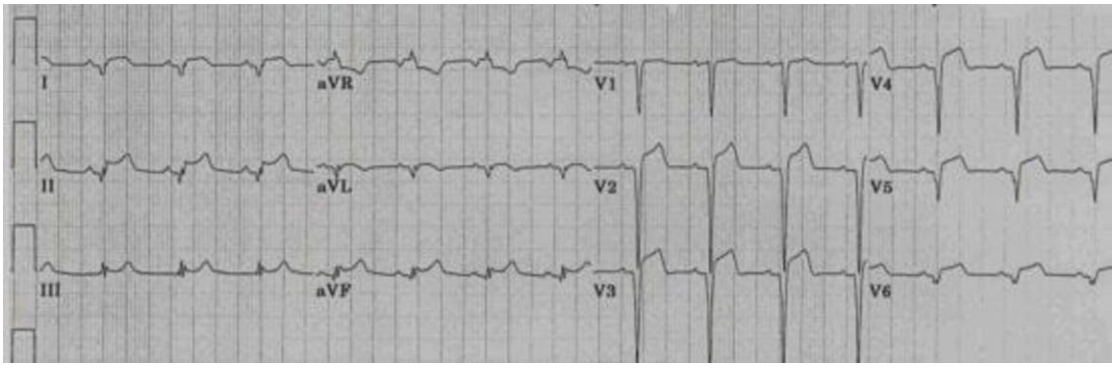
profile were within normal range. Electrocardiogram was done which showed normal sinus rhythm with normal QT interval depicted in Figure 1.

Figure 1: Electrocardiogram before staring clozapine therapy was normal.



We decided to start clozapine at a lower dose and increase it to 200 mg per day. After 3 weeks of clozapine therapy, the patient started complaining of sudden onset of chest pressure associated with palpitations, lethargy and dizziness. There were no other complaints associated with difficulty in breathing, fever, cough, vomiting, and diarrhoea. His blood pressure was 86/72 millimetres of mercury, heart rate was 114 beats per minute, and oxygen saturation was 98 percent. There was no past history of risk factors for cardiovascular disease. Routine investigations were performed, and it came within normal limits, but cardiac enzymes such as troponin increased and creatine kinase-MB (CK-MB) was panic 40 u/L, lactate dehydrogenase (LD or LDH) 27 u/L, and C-reactive protein (CRP) become positive. Urine analysis showed no signs of infection. His chest x-ray was unremarkable. An electrocardiogram was obtained, which showed ST elevation, and sinus tachycardia depicted in Figure 2.

Figure 2: Electrocardiogram during clozapine therapy shows ST elevation



Patient was referred to a cardiology consultation, and they withhold all his psychiatric medications. Two-dimensional echocardiography (2D echo) was performed, which revealed an ejection fraction of 40 percent. On the third day after discontinuation of clozapine, a 2D echo was performed again; it showed normal left ventricular function (LVF) and an ejection fraction (EF) of 65 percent with normal systolic functions. Later an electrocardiogram was performed, which was within normal limits, and all other laboratory investigations were within normal limits. On the basis of above-mentioned investigations, the patient was diagnosed with clozapine-induced myocarditis. The patient was transferred back to our hospital in stable condition for further management of his psychosis. Clozapine withdrawal can lead to rapid worsening of psychiatric symptoms, and the patient was resistant to other antipsychotics, so clozapine challenge has been considered but with caution. We re-started clozapine slowly under close monitoring of blood investigations

and electrocardiograms and increased the dose to 200 mg per day within two months. Our patient's psychiatric symptoms improved without an increase in cardiac enzymes, and his electrocardiogram was normal. Currently, the patient has been stable on 200 mg of clozapine for one year and is free of cardiac side effects and psychotic symptoms.

DISCUSSION

The reintroduction of clozapine after the development of clozapine-induced myocarditis is controversial, although there are some studies in which clozapine has been successfully reintroduced [7]. According to the researcher there are three factors that may influence the success of clozapine re-challenge after acute myocarditis, such as the severity of the original acute myocarditis, the time interval between the myocarditis event and re-challenge or the rate of clozapine dose titration during re-challenge. The patient we treated is a successful example of clozapine reintroduction after the development of clozapine-induced myocarditis.

The decision to restart clozapine should be discussed with the patient, family members, and a cardiologist. Cardiac functions and routine laboratory tests were assessed before starting clozapine treatment, and clozapine was restarted after normal results were obtained. In our patient, clozapine was re-started slowly within two months, and his dose was slowly increased over a longer period of time, 12.5 mg every three days. According to the standard protocol, the patient was closely monitored for cardiac and other adverse effects during the first eight weeks of treatment; weekly cardiac enzymes, electrocardiograms, two-dimensional echocardiograms, and routine blood tests were also performed [8].

Although controversial, some authors say that slow titration of clozapine gives good results and that there is no harm in restarting clozapine, or avoiding myocarditis with this strategy, and that rapid titration may trigger myocarditis in susceptible patients [9]. The researchers said that previously affected myocarditis patients appear not to be contraindicated to restarting clozapine therapy; however, they recommended starting carefully with low doses and appropriate monitoring. There is a thesis on acute myocarditis occurring mainly in the first 14 to 21 days after initiation of clozapine therapy [10] and in our patient it occurred in the third week after initiation of clozapine therapy.

CONCLUSION

Clozapine-induced myocarditis is always a misunderstood complication. Therefore, it is important to raise awareness as it is safest medication for treatment-resistant schizophrenia when appropriately and closely monitored. If clozapine-related myocarditis is suspected, a high threshold for re-challenge should be set. Clinical vigilance and knowledge of this potentially fatal adverse effect is essential introducing clozapine.

REFERENCES

1. Hennen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. Schizophr Res 2005;73:139-45.
2. Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 2006;63:622-9.
3. Siddiqui JA, Qureshi SF, Shawosh YB. Clozapine-induced massive hematemesis: A rare case report. Ann Indian Psychiatry 2019;3:171-2.
4. De Berardis D, Serroni N, Campanella D, Olivieri L, Ferri F, et al. Update on the adverse effects of clozapine: focus on myocarditis. Curr Drug Saf 2012;7:55-62.
5. Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A. Update onmyocarditis. J Am Coll Cardiol 2012;59:779-92.
6. Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999;354:1841-5.
7. Rosenfeld AJ, Gibbs T, Ivie R, Clarke L, Merrill DB. Successful clozapine retrial after suspected myocarditis. Am J Psychiatry 2010;167:350-1.
8. Hagg S, Spigset O, Bate A, Soderstrom TG. Myocarditis related to clozapine treatment. J Clin Psychopharmacol 2001;21:382-8.
9. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, Wolfe R, McNeil JJ. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: A case-control study. Schizophr Res 2012;141:173-8.

10. Haas SJ, Hill R, Krum H, Liew D, Tonkin A, Demos L, Stephan K, et al. 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;30:47-57.

****

Acknowledgements – Nil
Funding – Nil
Conflict of Interest - Nil