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Clozapine-induced myocarditis: Two case reports and review of clinical presentation and recognition

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Abstract

Myocarditis is a potentially fatal cardiac disease marked by inflammation of the heart muscle. With a noted black-box warning, rates of clozapine-induced myocarditis are reportedly as high as 3%. Since the first case of clozapine-induced myocarditis was documented in 1994, more than 250 cases have been described in literature with an approximate 33% case-fatality rate. We report 2 cases of patients with primary psychotic disorders treated with clozapine, who developed signs and symptoms of myocarditis. The first was a 35-year-old white male patient with a primary diagnosis of schizoaffective disorder (bipolar type) who was initiated on clozapine after nonresponse to several therapies. On day 26, the patient was admitted to the emergency department for chest pain presenting with eosinophilia and notable elevations in several biomarkers, including troponin and C-reactive protein. The second patient was a 45-year-old black male who was initiated on clozapine for treatment-resistant schizophrenia. On day 13, the patient reported cardiac-related concerns (tachycardia) and flu-like symptoms resulting in hospitalization. Similarly, this patient demonstrated elevated biomarkers (troponin and creatine kinase). Both patients experienced resolution of symptoms after discontinuation of clozapine. Clozapine was not rechallenged for either patient. Review of literature further elucidates the relationship between clozapine and myocarditis, including potential risk factors, pathophysiology, and symptom presentation. Due to the potentially fatal nature of this condition, clinical vigilance and awareness is warranted upon initiation of clozapine through monitoring of symptoms along with cardiac and inflammatory biomarkers as indicated.

Keywords: mental health, myocarditis, pharmacist, psychiatry, clozapine, schizophrenia, cardiomyopathy

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Background

Myocarditis is a potentially fatal disease marked by inflammation of cardiac muscle and is associated with 5% to 20% of all cases of sudden death in young adults.[1,2] Cardiac outcomes of myocarditis can range anywhere from fulminant heart failure to sudden cardiac death. Although primarily attributed to viral infections (>70% of

cases), noninfectious causes of myocarditis can include preexisting autoimmune disease, toxins (eg, carbon monoxide, arsenic, ethanol), and hypersensitivity to drugs.[2] Hypersensitivity to the second-generation antipsychotic clozapine is associated with both immune-mediated (induced inflammatory markers) and non–immune mediated (direct damage to myocardium) mechanism of myocarditis.[3-5] Estimates of absolute risk from regulatory data generally range from ~0.01% to 0.19% with rates as high as 0.7% to 3% reported in large cohorts.[6-8] Reported fatalities related to clozapine-induced myocarditis range from 10% to 46%.[9,10] The relatively high variability in these estimates may be partially due to underreporting of cases to regulatory agencies or, conversely, increased provider awareness of this potentially fatal adverse event.

We report 2 cases of patients with primary psychotic disorders treated with clozapine, who developed signs and symptoms of myocarditis. Additionally, a literature review summarizing case reports of clozapine-induced myocarditis is presented along with potential mitigation strategies for this adverse effect.

Case Report 1

A 35-year-old white male nonsmoker with schizoaffective disorder (bipolar type) reported to a residential substance use disorder treatment program for medication management after recent psychiatric hospitalization for worsening anxiety and auditory hallucinations. Patient has a past psychiatric history of stimulant use disorder (methamphetamine), sedative/hypnotic/anxiolytic use disorder (clonazepam), and alcohol use disorder. Other notable comorbidities include hypothyroidism, hypertension, and hyperlipidemia. Despite compliance with a current psychotropic regimen, patient presented with ongoing psychosis and was started on clozapine 12.5 mg twice daily. Previous antipsychotic trials include lurasidone, quetiapine, aripiprazole, and risperidone. His current medications include divalproex ER 2000 mg daily (steady-state serum concentration = 98.7 mcg/mL), duloxetine 60 mg daily, hydroxyzine 50 mg 3 times daily as needed for anxiety, propranolol 40 mg twice daily, levothyroxine 0.2 mg daily, omeprazole 20 mg daily, and amlodipine 2.5 mg daily. Clozapine was titrated at 25 mg/day increments to 100 mg twice daily without incident. On day 26 of clozapine therapy, the patient notified the nursing staff that he was experiencing abdominal and chest pain, described as "stabbing" left-sided chest pain with a severity of 8/10. He denied any pain radiating to jaw, neck, or left upper extremities but did report numbness to left phalanges and persistent sore throat. The patient was then transferred to the emergency department for further evaluation.

After cardiac workup, results were significant for tachycardia and eosinophilia with elevations in troponin levels, brain natriuretic peptide, D-dimer, erythrocyte sedimentation rate, and C-reactive protein (CRP; see the Table). Echocardiogram was unremarkable with a normal ejection fraction. Chest x-ray was also unremarkable. Of note, patient denied current use of any illicit substances, and urine drug screen was negative upon admission. There were no electrocardiogram (ECG) changes, all other labs and vitals were within normal limits, and other medical causes (ie, pulmonary thrombosis, acute coronary syndrome, and viral myocarditis) were ruled out. Clozapine was discontinued due to potential myocarditis along with duloxetine and divalproex (due to potential contribution to chest pain and palpitations). The patient was empirically treated for myocarditis with intravenous fluids and oral prednisone taper over 1 week. Over the next 5 days, the patient symptomatically improved, and biomarkers slowly returned to normal values. Clozapine, the suspected etiological factor, was permanently discontinued, and quetiapine was reinitiated for management of psychosis without any further incidents.

Case Report 2

A 45-year-old black male nonsmoker with a history of schizophrenia and gastroesophageal reflux disease was initiated on clozapine 25 mg at bedtime for treatment-resistant schizophrenia on an acute unit at a state psychiatric facility. Previous psychotropic trials include olanzapine, haloperidol, and quetiapine. The patient's clozapine dose was titrated to 250 mg twice daily over 12 days (increase by 25 to 50 mg daily) with no noted side effects. Other medications at that time included acetaminophen 650 mg 3 times daily as needed for pain, docusate calcium 240 mg twice daily, lidocaine patch 5% daily, multivitamins, pantoprazole 40 mg daily, and polyethylene glycol 17 g daily. On day 13 of clozapine therapy, the patient was noted to have intermittent bilateral hand tremors, diaphoresis, tachycardia (heart rate = 134 beats/min), and an elevated temperature (100.2°F, oral). The patient reported neck and jaw stiffness. Propranolol 20 mg 3 times daily was initiated for tremors and tachycardia. Two days later, the patient endorsed dizziness, headache, and neck pain. Additionally, the patient reported nasal congestion; however, lungs were clear upon auscultation; no oropharyngeal lesions were observed. On the following day, the patient continued to experience tachycardia (heart rate = 132 beats/min) and fever (100.7°F) and, thus, was transferred to a local hospital for further evaluation. Cardiac and inflammatory biomarkers obtained during admission revealed elevated troponin and creatine kinase-MB isoenzyme (see the Table). Electrocardiogram readings displayed ST elevation with possible early repolarization.

TABLE: Patient presentation of laboratory markers and assessments upon acute admission

Laboratory Marker/Assessments	Patient 1	Patient 2	Reference (Normal) Range
Laboratory marker			
Heart rate, beats/min	122	200	60 to 100
Troponin levels, ng/mL	0.16	4.8	<0.03
Brain natriuretic peptide, pg/mL	217	Not obtained	0 to 100
D-dimer, ng/mL	270	Not obtained	0 to 230
Creatine kinase-MB isoenzyme, U/L	Not obtained	1627	0 to 215
Erythrocyte sedimentation rate, mm/h	72	Not obtained	<30
C-reactive protein, mg/L	12.83	Not obtained	0 to 1.0
Eosinophils, %	7.3	3	0.0 to 6.0
Additional assessments			
Echocardiogram, %	Unremarkable (EF = 60 to 65)	Unremarkable (EF = 65 to 70)	EF = 55 to 70
Electrocardiography	Regular rate and rhythm with no electrocardiac changes	Atrial fibrillation with rapid ventricular rate; ST elevation with possible early repolarization	Regular rate and rhythm with no electrocardiac changes

EF = ejection fraction.

Echocardiogram was unremarkable, and urine drug test was negative. Acute coronary syndrome was ruled out; however, the patient was noted to be in atrial fibrillation with rapid ventricular rate. The patient was then transferred to the intensive care unit for treatment. After 5 days of admission, myocarditis secondary to medications was suspected, and clozapine was discontinued. The patient received supportive care (intravenous fluids and acetaminophen as needed for pain) and became medically stable on day 5. The patient was transferred back to the psychiatric hospital and managed on olanzapine 30 mg daily for psychosis. Cardiology follow-up 10 days later showed normal creatine phosphokinase, troponin, CRP, and complete blood count.

Discussion

The presented cases describe 2 patients who experienced myocarditis and cardiac complications probably related to clozapine use. Neither patient had a prior history of cardiac complications or preexisting conditions that may have predisposed them to myocarditis (eg, autoimmune disease, toxin exposure). Additionally, infectious etiology (ie, Coxsackie virus) was ruled out. Of note, the first patient had a prior history of chronic stimulant use, which may also cause long-term heart damage; however, previous ECG reports did not suggest any preexisting heart defects. The temporal association of cardiac symptoms and laboratory abnormalities with clozapine administration suggests a high likelihood of clozapine etiology for both patients. Furthermore, assessment with a Naranjo rating scale indicates a high probability of clozapine being the offending agent in both cases.[11]

A review of the literature was conducted using PubMed, ScienceOpen, and Google Scholar databases through May 2018 to evaluate components of clozapine-induced myocarditis. The search terms included *clozapine*, *myocarditis*, and *adverse effects*.

Since the first case of clozapine-induced myocarditis was documented in 1994, more than 250 cases have been described in literature with an approximate 33% case-fatality rate.[4,12] The majority of cases included relatively young male patients between the ages of 27 and 46 years of age.[10] The true incidence of clozapine-induced myocarditis may be higher than reported as many symptoms nonspecific to myocarditis (ie, tachycardia, hypotension, fatigue) are often considered benign side effects of clozapine dose titration.[8-10,12]

The mechanism of clozapine-induced myocarditis is not fully understood; however, it is largely hypothesized to be a type 1 hypersensitivity reaction (immunoglobulin E–mediated), leading to inflammation of the heart muscles.[8,13] This is supported by common observations of peripheral eosinophilia and eosinophilic inclusions within endomyocardial biopsy samples of affected patients.[8,13,14] Other proposed non–immune mediated mechanisms associated with clozapine-induced myocarditis include anticholinergic M2 receptor blockade, release of proinflammatory cytokines, direct toxic effect on the myocar-

dium leading to inflammatory infiltrate, and increased serum catecholamine levels.[15] There are also reports of a potential genetic predisposition although no particular markers have been identified to date.[14]

Myocarditis typically appears within the first 6 months of clozapine therapy with 85% to 90% of cases estimated to occur within 8 weeks of initiation.[8,14-16] A particularly high incidence in the third week of treatment has been reported in literature,[8] which is consistent with both presented cases. Presenting symptoms include acute chest pain, dyspnea, palpitations, flu-like symptoms (fever, fatigue, sore throat), and gastrointestinal disturbances (nausea, vomiting, diarrhea).[8-17] According to a recent systematic review[18] analyzing 82 cases of clozapine-induced myocarditis, symptoms and signs of myocarditis developed in 87% of patients within the first month with clinical presentations to include shortness of breath (67%), fever (67%), and tachycardia (58%). Physical signs commonly include tachycardia, ECG changes (specifically, ST-segment elevation and/or T-wave inversions), impaired left/right ventricular function, elevated troponin and/or creatine kinase-MB, eosinophilia, and elevated inflammatory biomarkers (ie, CRP, erythrocyte sedimentation rate [ESR]).[8-18] Both patient cases presented quite similarly in regards to clinical symptoms (acute chest pain, palpitations, and flu-like symptoms), and both patients demonstrated an elevation in inflammatory markers, particularly troponin levels. However, only the first patient presented with eosinophilia along with elevations in CRP, ESR, and D-dimer. Cardiomyopathy is a secondary outcome of myocarditis; however, clozapine use can be an independent risk factor for its development (often delayed reaction occurring after ~8 months of treatment).[6] Full discussion of cardiomyopathy secondary to clozapine is beyond the scope of this manuscript; nonetheless, early assessment of both presented cases' ECGs did not indicate development (or early signs) of cardiomyopathy. Additionally, it is important to note that there were differences in ECG findings between the 2 patients. The first patient displayed normal readings, and the second patient experienced ST-elevations. Literature suggests ECG changes in the setting of myocarditis is commonly associated with cardiomyopathy; however, a normal reading does not rule out the possibility for the disease.[8,14]

A number of phenotypic and dose-related factors have been proposed as predictors of clozapine-induced myocarditis. This includes a higher risk in young male patients between the ages of approximately 20 to 40 years old.[10,18-21] Some reports[8,10] suggest clozapine-associated myocarditis is dose-dependent, and others describe occurrences at standard and even low doses (12.5 mg to 300 mg total daily dose), such as the cases presented here. Rapid titration (rate greater than 25 to 50 mg dose increase per day) may increase risk of clozapine-induced myocarditis.[19,20] In a study[21] evaluating risk factors associated with clozapine-induced myocarditis, the authors cite a 25% increase of myocarditis risk for every 250 mg cumulative increase within the first 9 days.

There are varying reports suggesting an increased risk of myocarditis when clozapine is coadministered with certain psychotropic agents.[19,20] According to an evaluation of 105 cases by Ronaldson et al,[21] concomitant sodium valproate more than doubled the risk of developing myocarditis (potentially related to competitive inhibition of cytochrome P450 enzyme between the 2 agents). In another study by Yousseff et al,[22] which included 129 clozapine-treated patients, risk of myocarditis increased more than 6-fold with concomitant selective serotonin reuptake inhibitor use, and use of other antipsychotics, benzodiazepines, other antidepressants, or sodium valproate and derivatives were not found to increase risk. Although intriguing, the major limitation of this study was the low number of cases identified ($n = 5$).

Due to the severity and often unrecognized symptoms of clozapine-induced myocarditis, it is important to implement strategies to appropriately manage this condition. As a result of an increased incidence of occurrence within the first 8 weeks of therapy, diligent monitoring of both cardiac and nonspecific symptoms is essential during this time period. Although there are no standard protocols, the Australian treatment guide proposed by Ronaldson et al[23,24] recommends monitoring for potential myocarditis through baseline and weekly (for the first month) assessments, including vitals, laboratory evaluation of peripheral eosinophils, CRP, ECG, and troponin levels. According to an evaluation of 75 cases by Ronaldson et al,[24] troponin more than twice the upper limit of normal or CRP over 100 mg/L was associated with 100% sensitivity for symptomatic clozapine-induced myocarditis. Assessment of other inflammatory biomarkers including brain natriuretic peptide, ESR, and creatine kinase-MB may also be considered during this period; however, it is not a widely accepted approach due to their low specificity for myocarditis.[12,23] Abnormalities in these blood parameters, usually with corresponding clinical symptoms, suggest potential myocarditis and may indicate the need to interrupt clozapine therapy and consult cardiology for further evaluation and formal diagnosis.[12,24] Given there is no standard monitoring protocol for clozapine-induced myocarditis, it is important to employ clinical judgment and utilize best practices based on individual hospital policies. With timely diagnosis and cessation of clozapine, the prognosis of mild cases that do not require supportive therapy is excellent with complete recovery of global cardiac function.[12,24] There is a risk of rapid psychiatric deterioration and cholinergic rebound upon abrupt discontinuation of clozapine; thus, compensatory psychiatric interventions should be in place.

Follow-up by cardiology for several weeks after resolution of myocarditis should be considered. If clozapine is highly suspected to be the cause of myocarditis, it is not recommended to rechallenge the patient due to the high risk of recurrence.[25-27] However, a few cases have identified successful rechallenge in the presence of close cardiac monitoring.[25] With the paucity of information on potential risk factors and variability in data regarding potentiation of risks with other medications, preventative measures for clozapine-induced myocarditis is limited beyond monitoring and aforementioned mitigation strategies.[17-24]

Conclusion

Clozapine-induced myocarditis is an often under-recognized complication of an otherwise very effective agent for treatment of refractory schizophrenia. Studies have shown a high incidence of occurrence within the first 8 weeks of treatment and comprise a wide spectrum of clinical presentations ranging from very nonspecific symptoms (which often mirror known adverse effects of clozapine titration) to fulminant heart failure and/or sudden cardiac death. Clinical vigilance and awareness of this potentially fatal adverse effect is necessary upon initiation of clozapine through monitoring of symptoms along with cardiac and inflammatory biomarkers as indicated. Suspicion of clozapine-related myocarditis usually warrants immediate discontinuation with a high threshold for rechallenge. Moreover, the heterogeneity of myocarditis presentation underscores the importance of early recognition and response by clinicians who are managing patients on clozapine therapy.

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