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A 25-Year-Old Man with Refractory Schizophrenia and Clozapine-Induced Myocarditis Diagnosed by Non-Invasive Cardiovascular Magnetic Resonance

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Male, 25-year-old
Final Diagnosis: Clozapine-induced myocarditis
Symptoms: Elevated troponin • fever • leukocytosis • somnolence • tachycardia
Medication: —
Clinical Procedure: Cardiovascular magnetic resonance • electrocardiogram • transthoracic echocardiogram
Specialty: Cardiology • General and Internal Medicine

Objective: Rare disease

Background: Clozapine, a second-generation antipsychotic, is often prescribed for refractory schizophrenia; however, it can cause life-threatening adverse events including agranulocytosis and myocarditis. Making the diagnosis of clozapine-induced myocarditis can be challenging given the non-specific presentation as well as risk involved in obtaining an endomyocardial biopsy. As clozapine-induced myocarditis carries a mortality risk of up to 30%, timely recognition, diagnosis, and management are vital. This report presents a case of clozapine-induced myocarditis in a 25-year-old man with refractory schizophrenia who was diagnosed using non-invasive imaging with cardiovascular magnetic resonance (CMR).

Case Report: A 25-year-old man with refractory schizophrenia was admitted with severe psychotic symptoms and started on a rapid titration of clozapine. During his hospitalization he developed somnolence, fever, and tachycardia with leukocytosis, elevated inflammatory markers, and cardiac biomarkers concerning for clozapine-induced myocarditis. Alternative etiologies were ruled out and CMR was used to confirm the diagnosis. The patient's symptoms resolved following discontinuation of clozapine and initiation of supportive therapies.

Conclusions: Clozapine-induced myocarditis is challenging to diagnose due to a lack of consensus on diagnostic criteria, reliance on voluntary reporting, and non-specific presentation. This report highlights that myocarditis can be associated with clozapine pharmacotherapy in patients with schizophrenia and demonstrates the value of diagnosis using non-invasive CMR. Additional studies are needed to understand the mechanism of clozapine-induced myocarditis and how clozapine titration may affect risk.

Keywords: Clozapine • Drug-Related Side Effects and Adverse Reactions • Magnetic Resonance Imaging • Myocarditis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/930103

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Background

Clozapine, a second-generation antipsychotic, can treat refractory schizophrenia, decrease hospital admissions, and improve levels of independent living [1]. It is, however, associated with agranulocytosis and myocarditis [1]. Making the diagnosis of clozapine-induced myocarditis, which has a mortality rate of 10-30% [2], can be challenging given the non-specific presentation as well as risk involved in obtaining an endomyocardial biopsy [3]. The case definition proposed by Youssef et al includes a temporal relationship with the initiation of clozapine, along with the presence of at least 1 symptom, including chest pain, flu-like symptoms, persistent tachycardia, and signs of heart failure (eg, S3, bibasilar crackles, and peripheral edema), and at least 1 abnormal diagnostic test result, including troponin greater than at least 2 times the upper limit of normal, transthoracic echocardiogram with systolic dysfunction, evolutionary T-wave inversions, or greater than 1 mm ST-segment deviation in at least 2 contiguous leads on EKG [4]. Multiple studies demonstrated a high proportion of patients with elevated CRP that preceded peak troponin levels as well as peripheral eosinophilia; however, clozapine-induced myocarditis can occur in the absence of both [5,6]. Previously published case reports demonstrate a variety of presentations, including chest pain and flu-like symptoms, along with elevated cardiac and inflammatory biomarkers within the first 4 weeks of clozapine initiation. A presumed diagnosis of clozapine-induced myocarditis was made in each of these cases after ruling out competing etiologies, providing supportive therapy, and observing a resolution of symptoms following clozapine discontinuation [7,8]. Systematic reviews on adverse reactions to clozapine suggest that the diagnosis of clozapine-induced myocarditis may frequently be missed due to non-specific presentation, range of symptom severity, limited cardiovascular investigation, and sudden death [1,3,9]. The criterion standard for diagnosing myocarditis was previously endomyocardial biopsy, which has become less favored given the risk of perforation (1/250) and death (1/1000). Furthermore, its sensitivity is limited by the transient nature of inflammatory infiltrates, and pathologists frequently disagree on interpretation of the biopsy specimens [10].

Use of cardiovascular magnetic resonance (CMR) provides an alternative, non-invasive method for diagnosis [4]. Current guidelines for the diagnosis of acute myocarditis with CMR, referred to as the "Updated Lake Louise Criteria", recommend using a combination of T2-weighted findings and increased myocardial T1, extracellular volume, or late gadolinium enhancement to demonstrate evidence of myocardial edema and nonischemic myocardial injury, respectively [11-13]. Given the high risk of mortality, recognizing, diagnosing, and managing clozapine-induced myocarditis in a timely fashion is vital. This report presents a case of clozapine-induced myocarditis in a 25-year-old man with refractory schizophrenia who was diagnosed using non-invasive imaging with cardiovascular magnetic resonance.

Case Report

A 25-year-old man with schizophrenia was started on clozapine for severe psychotic symptoms after failure of haloperidol, risperidone, and olanzapine. Clozapine was increased from 12.5 mg to 250 mg daily over 10 days, with symptom improvement, and then to 300 mg due to subtherapeutic serum levels (287 mcg/L, therapeutic reference range: 350 to 600 ng/mL). A week later, he became somnolent and febrile (40.3°C), with tachycardia (140 beats per second). He had no chest pain. The physical exam was unremarkable. The electrocardiogram (EKG) revealed diffuse ST-segment elevations (STE) without reciprocal changes, suggestive of pericarditis (**Figure 1**). Lab test results showed leukocytosis (12 600 cells/mm^3, reference range 3800-10 600 cells/mm^3) without eosinophilia, elevated inflammatory (C-reactive protein 19.9 mg/dL, reference range <0.8 mg/dL; erythrocyte sedimentation rate of 91 mm/h, reference range 0-23 mm/h), and cardiac biomarkers (troponin 17.53 ng/mL, reference range <0.1 ng/mL). A transthoracic echocardiogram (TTE) showed a small pericardial effusion and was otherwise normal.

The clinical constellation of tachycardia, fever, elevated inflammatory markers, and diffuse STE within 2 weeks of starting clozapine was suggestive of clozapine-induced myocarditis, a recognized adverse effect. CMR showed diffuse epicardial and patchy myocardial late gadolinium enhancement with edema on T2-weighted imaging (**Figure 2**). Left ventricular ejection fraction was 38%. There was no pericardial thickening or enhancement to suggest pericarditis. An infectious workup was negative. Within 48 hours of clozapine discontinuation, the fever, tachycardia, and leukocytosis resolved. He was started on supportive therapy including colchicine [14], lisinopril, and metoprolol [1].

Discussion

CMR enables prompt diagnosis and management of clozapine-induced myocarditis, a potentially fatal complication of clozapine therapy, in a non-invasive manner. The incidence of clozapine-induced myocarditis (0.7-8.5%) varies widely due to the lack of consensus on diagnostic criteria, reliance on voluntary reporting, and non-specific presentation [4]. Infections, autoimmune disease, and ischemia may need to be excluded. Case reports published by Sackey et al ruled out alternative etiologies and demonstrate improvement following clozapine discontinuation; however, one case involved the discontinuation of other potential contributing medications and the other

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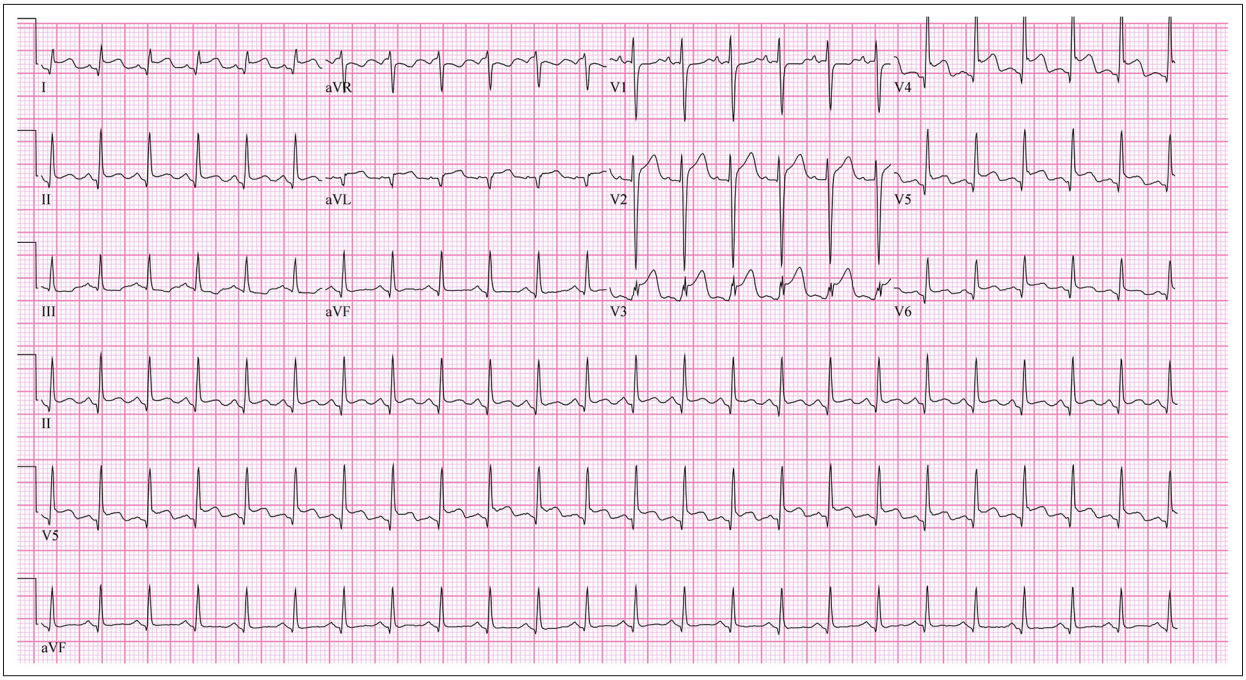

Figure 1. Electrocardiogram (EKG) while the patient experienced tachycardia without chest pain. EKG demonstrated sinus tachycardia with diffuse ST-segment elevations that were most prominent in the anteroseptal leads. These findings were concerning for ischemia versus pericarditis versus myocarditis.

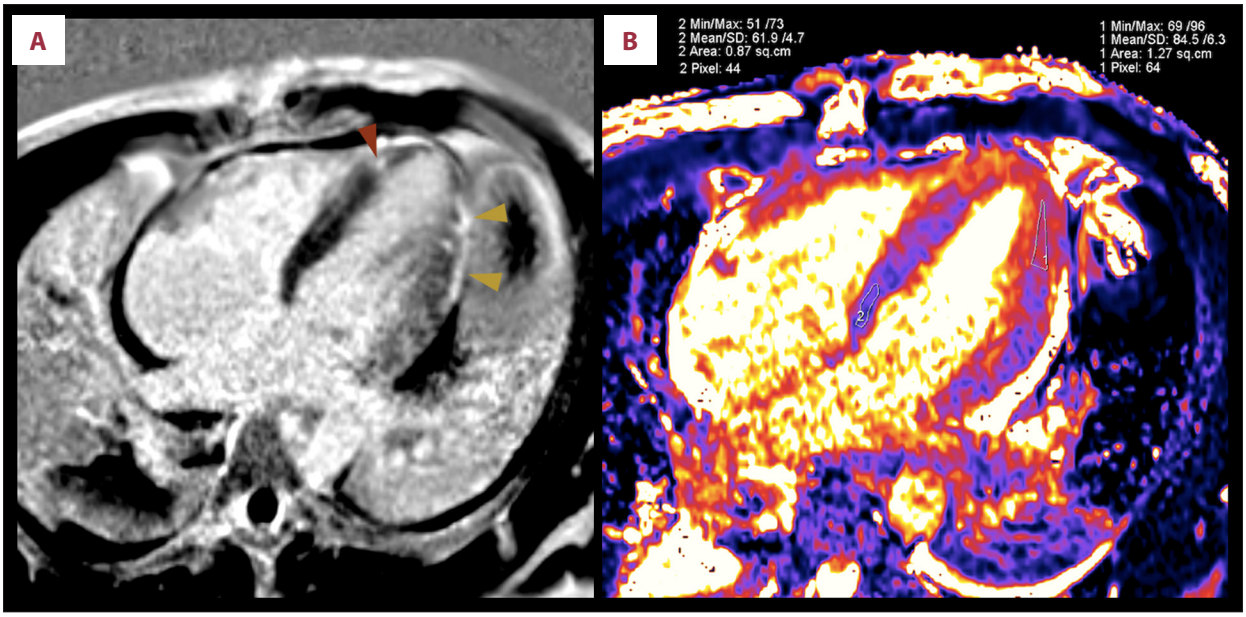

Figure 2. Cardiovascular magnetic resonance (CMR) demonstrates myocardial changes that reveal the diagnosis. (**A**) Late gadolinium enhancement CMR revealed acute myocarditis as evidenced by epicardial necrosis and edema of the middle and apical lateral wall (yellow arrowheads), as well as small foci of mid-myocardial necrosis in the apical septum (red arrowheads). (**B**) Direct T2 quantification confirmed the presence of myocardial edema indicative of acute ischemia in these regions, measuring 84.5±6.3 ms (Region 1), compared with 61.9±4.7 ms in healthy non-ischemic myocardium (Region 2). These findings support the diagnosis of clozapine-induced myocarditis.

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identified the presence of atrial fibrillation with rapid ventricular response that required an ICU admission and supportive therapy. Neither case confirmed the presence of myocardial inflammation with imaging or endomyocardial biopsy [8]. In the case reported by Datta et al, the diagnosis of clozapine-induced myocarditis was highest on the differential diagnosis after ruling out obstructive coronary artery disease with cardiac catheterization and common causes of infection. However, they note that they did not rule out illicit substance use and that use of CMR to confirm the diagnosis would have been beneficial [7]. We followed a similar approach in evaluating our patient's symptoms; however, CMR confirmed the diagnosis using the updated Lake Louise Criteria [13]. This provided increased confidence that the patient was receiving the most appropriate therapy to resolve his symptoms and reduce risk of recurrence. The timely discontinuation of clozapine along with supportive care led to an improvement in symptoms for our patient, as well as those previously described.

Non-invasive diagnosis of myocarditis by CMR (84% sensitivity, 74% specificity, and diagnostic accuracy of 79%) has replaced endomyocardial biopsy [15]. The majority of clozapine-induced myocarditis cases (75%) develop within the first month of use, which was true in our case and the previously published cases described above. Bellissima et al reported that the median dose at presentation was 250 mg/day, with the most common presenting symptoms being fever (67%), dyspnea (67%), and tachycardia (58%) along with elevated cardiac biomarkers (87%) [1]. The mechanism by which clozapine causes myocarditis is poorly understood. One hypothesis is that cardiotoxicity may be due to a type-1 hypersensitivity reaction resulting in myocardial damage and inflammatory infiltrate, perhaps as a result of rapid titration. However, case review by the Toronto Forensic Pathology Unit found that most inflammatory infiltrates were not eosinophilic [16]. Alternatively, cardiotoxicity could be due to a type-3 allergic reaction or direct toxic effect of clozapine or its metabolites. Another hypothesis is that clozapine accumulates to toxic levels due to unfavorable pharmacogenetics such as CYP450 1A2, 1A3, and CYP2C19 poor metabolizers or enzyme deficiency [17]. A case-control study found that the risk of clozapine-induced myocarditis increased by 26% per 250 mg administered over the first 9 days of titration (OR 1.26, 95% CI 1.02-1.55, *P*=0.03) [18]. Our patient received therapy consistent with FDA guidelines, which suggest titration up to 300 mg to 450 mg daily over the course of 2 weeks, resulting in a cumulative dose of 2075 mg at the onset of his tachycardia [19]. Australian guidelines recommend slow titration of clozapine over 2 weeks to a dose of 200 mg daily, with a cumulative dose of less than 1500 mg, with subsequent increases capped at 100 mg weekly [20]. For the first 18 weeks of therapy, weekly monitoring for agranulocytosis is required [1]. While routine monitoring for clozapine-induced myocarditis may be precluded by resource availability [21], this case illustrates the use of CMR for this difficult diagnosis.

Conclusions

This report highlights that myocarditis can be associated with clozapine treatment in patients with schizophrenia and demonstrates the value of diagnosis using non-invasive CMR. This approach enables prompt diagnosis and management without the risk of an endomyocardial biopsy. Additional studies are warranted to establish whether rapid titration is a risk factor for clozapine-induced myocarditis.

Conflict of Interest

None.

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