

Clozapine induced Myocarditis: Atypical Presentation and Diagnostic Difficulties

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Abstract

We describe a case of a 21-year-old man who developed Clozapine induced myocarditis (CIM), an uncommon, but serious and potentially life threatening, side-effect of Clozapine. The case is unusual because of presentation was atypical (symptoms, age, and time frame of symptom-evolution), which increased the risk of the adverse event being missed. This report highlights the difficulties in the diagnosis of CIM in psychiatric patients with atypical presentations. A combination of unreliable history, uncertainties about risk factors and absence of consensus guidelines about the speed of Clozapine titration. Clinicians are often unaware of the risk factors for myocarditis. Currently there is no mandatory requirement of laboratory monitoring for detecting myocarditis during Clozapine titration, unlike that for detecting neutropenia. The case report throws into sharp relief the need for vigilance and high index of suspicion during Clozapine titration. A protocol is suggested for close clinical monitoring and laboratory investigations during Clozapine titration, which will increase the chances of early detection and treatment of CIM, thus reducing the risk of high mortality.

Keywords: Clozapine, myocarditis, diagnosis, troponin, CRP

Abbreviations: CIM - Clozapine induced myocarditis; ECG - Electrocardiogram; CRP - C-reactive protein; BPM - beats per minute; BNP - Brain natriuretic peptide; NTproBNP - N-Terminal pro-B-type natriuretic peptide; EBV - Epstein Barr virus

Introduction

Clozapine is an atypical antipsychotic, it is the treatment of choice for treatment resistant schizophrenia and more effective than conventional neuroleptic medications. Clozapine is associated with potentially life-threatening side effects, some of which appear early in treatment.

Myocarditis is an uncommon but serious early adverse event of Clozapine, the majority of reported cases occurring in the first 4-8 weeks.¹ Clozapine induced myocarditis (CIM) can present with mild symptoms, but can progress rapidly to fulminant symptoms and thereafter heart failure and death.¹ These symptoms and signs typically include dyspnoea, palpitations, chest pain, fatigue, flu-like symptoms, pyrexia and tachycardia.

Case Report

A 21-year-old Caucasian male with a two year diagnosis of schizophrenia and previously inadequate responses to Risperidone and Olanzapine was commenced on Clozapine. The patient had previously tolerated Risperidone and Olanzapine and did not experience adverse events, but there was inadequate therapeutic response to both; hence it was decided to commence Clozapine.

On admission, his physical examination, baseline blood investigations (these did not include cardiac markers such as troponin or C-reactive protein (CRP)) and electrocardiogram (ECG) were normal. His medical history was unremarkable and he did not have a family history of cardiac disease. He smoked 15 cigarettes per day.

A rapid Clozapine titration compared with the standard UK titration² was commenced with a target dose of 200 mg/day on day 14. He was not on any other psychotropic medication.

The patient remained asymptomatic in the first 3 days. On day 4, he developed tachycardia (114 BPM). A repeat physical examination and ECG was normal, eventually his heart rate settled to 94 BPM. The tachycardia was deemed to be a benign side effect of Clozapine, and the rate of titration was slowed down as a precaution.

On day 12, the patient reported dizziness when standing and a 'cold air' sensation in his chest. Nurses reported that blood pressure was normal with a heart rate of 145 BPM but when reviewed clinically his heart rate was 89 BPM. His titration was continued.

On day 14, the patient complained that his 'internal organs were hurting'. His Clozapine dose was 125 mg/day at the time. He reported chest tightness with central pain, pain in his legs and abdomen, intermittent breathlessness and palpitations. The duration of his symptoms was 24-36 hours. Examination was normal except for a heart rate of 110 BPM. His ECG showed sinus rhythm with no ST segment or T wave changes. Blood tests showed markedly elevated troponin I—1211.5 ng/L (normal range: <34.3 ng/L), CRP—176 mg/L (normal range: 0-10 mg/L) and eosinophil count —1.28 10⁹/L (normal range: 0.02-0.5 10⁹/L).

The patient was afebrile throughout the titration period.

He was admitted to an acute hospital and a provisional diagnosis of Clozapine induced myocarditis was made. The echocardiogram did not reveal structural abnormalities or damage. An EBV (Epstein Barr Virus) serology was negative. Clozapine was withheld and the patient improved along with the blood markers, after 4-5 days he was discharged back to the psychiatric hospital.

Discussion

CIM is an often overlooked adverse event associated with Clozapine titration. Currently there is no mandatory requirement of laboratory monitoring for detecting myocarditis during Clozapine titration unlike the mandatory requirement for detecting neutropenia, despite roughly similar estimated incidence of the two adverse events at 3%.^[3,4]

This case was unusual because of the very early appearance of symptoms, the patient's age and atypical symptom presentation. Although CIM is an early adverse event, the onset within 2 weeks of initiation was unusual. Literature suggests that myocarditis typically presents within 4-8 weeks.^[1] The patient was also younger than the reported median age of patients (30).^[1] The symptoms appeared at a low dose of 125mg/day which literature suggests is unusual, although CIM at doses of 50mg/day has been reported.^[5]

Tachycardia and fever are common early side-effects of Clozapine. Tachycardia usually settles after 4-6 weeks of treatment^[6] and fever typically for 2-3 days.^[7] Both symptoms can be suggestive of myocarditis, especially when they co-occur. CIM often presents in a non-fulminant form.^[8] As this case demonstrates many patients may not report symptoms when CIM is mild.

Increasing age, concomitant administration of sodium valproate and increased rate of dose titration are significant risk factors for CIM.^[9] In this case, the patient was young and sodium valproate was not co-administered. The titration was originally intended to be rapid but slowed down soon after commencement.

Given the clinical difficulties in detecting mild CIM, we suggest that all patients have baseline troponin, CRP, heart rate, blood pressure, temperature, respiratory rate and ECG. If medical history reveals history of heart disease, a baseline echocardiogram can be obtained. If there is history of congestive cardiac failure, then baseline brain natriuretic peptide (BNP) or N-Terminal pro-B-type natriuretic peptide (NTproBNP) should be measured.^[10]

In clinically asymptomatic patients, if there is elevated baseline CRP (>100 mg/L), troponin, BNP or NTproBNP then Clozapine titration should not commence and further advice from cardiology should be sought.

Weekly CRP and troponin should be done in the first month of titration and levels repeated once after stable dose of Clozapine is reached. The dose increase should not be rapid.

Tachycardia developed should be checked with reference to the baseline heart rate measured before commencing Clozapine. A heart rate of greater than 120 BPM or increase of more than 20 BPM over the baseline pulse rate should lead to the review of physical health, blood monitoring, ECG, and Clozapine titration rate.

An increase in troponin above upper limits or an increase in CRP should trigger consideration of CIM. Literature suggests that troponin levels greater than 2x the upper normal limit are indicative of acute myocarditis.^[9] CRP is raised on average 3 days before any increase in troponin levels is detected.^[9] If the troponin levels are within the normal range and the CRP levels are raised but less than 100 mg/L, clozapine titration can continue, but the pace must be slowed. Troponin levels and CRP levels should be monitored daily and the patient should be closely monitored for clinical signs of developing cardiotoxicity.

We do not recommend routine eosinophil monitoring as the marker in 90% of cases does not exceed normal limits at the onset of CIM and typically peaks 7 days after cessation of Clozapine.^[11]

Conclusion

Clozapine induced myocarditis often presents with low level cardiotoxicity. Mild symptoms may be missed; however, progression to fulminant myocarditis can be rapid, with high mortality rates.^[1] Myocarditis, including clinically asymptomatic myocarditis remains a risk with Clozapine every time the patient is titrated onto this medication^[12]. Close clinical monitoring, high index of suspicion and monitoring of cardiac parameters will help early detection of adverse cardiac events.

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Competing Interests

None declared

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