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Case Report

Recognizing the Warning Signs for the Timely Diagnosis and Treatment of Clozapine-Induced Myocarditis: A Case Report

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Abstract

Clozapine-induced myocarditis (CIM) is defined pathologically as an inflammatory disorder of the myocardium. An accurate diagnosis of clozapine-induced cardiotoxicity is challenging due to the heterogeneous symptomatology and nonspecific features of myocarditis. Consequently, a high index of suspicion of CIM is required for a proper and timely diagnosis. The following case report highlights a 25-year-old African American male with 1) no initial abnormal cardiac biomarkers, 2) a recurrence of mania with psychotic features, leading to 3) a diagnosis of biplolar I disorder (BID), and 4) failed trials of antipsychotics. Without behavioral improvement through antipsychotics, the patient's care team decided to initiate clozapine as a last resort. The patient's behavior significantly improved; however, nonspecific features began to arise, such as the patient complaining of flu-like symptoms, nausea, vomiting, diarrhea, body aches, chills, and fatigue; and EKG results indicating abnormal ventricular depolarization and repolarization.

The patient's plethora of nonspecific symptoms and cardiovascular condition deteriorated progressively, which subsequently resulted in heart failure and required stabilization with mechanical ventilation. After the patient was stabilized, he was seen by a cardiologist who diagnosed the patient with drug-induced myocarditis and promptly discontinued the patient's clozapine. CIM is a rare condition that presents with nonspecific features; moreover, an accurate diagnosis is challenging. The following case report highlights the importance of identifying possible symptoms occurring in CIM, and factors involved in overcoming issues related to its diagnosis. Heightened suspicion regarding the use of clozapine may lead to a timely diagnosis of CIM which can have a dramatic effect on treatment outcome.

Keywords: *Antipsychotic Agents; Adverse Effects; Bipolar Disorder; Cardiac Biomarkers; Clozapine; Clozapine-Induced Myocarditis; Heart Failure; Myocardial Infarction*

Abbreviations

BID: Bipolar I Disorder; BNP: B-Type Natriuretic Peptide; CIM: Clozapine-Induced Myocarditis; cMRI: Cardiac Magnetic Resonance Imaging; LV: Left Ventricular; REMS: Risk Evaluation and Mitigation Strategy

Preface

The main objectives of the following case report are as follows:

- To review the use of clozapine (an atypical antipsychotic) in the treatment of schizophrenia.
- To support a working knowledge of the current guidelines for the early detection of symptoms of myocarditis.

- To better monitor patients receiving clozapine.
- The enhance the care provider's ability to identify early clinical signs and symptoms of CIM.
- To provide a deeper understanding of the new clozapine risk evaluation and mitigation strategy (REMS) for detecting clozapine-related neutropenia.
- To provide a review of other clozapine-related complications.

Introduction

Inflammation of the myocardium, the middle layer of the heart wall, is typically associated with clozapine-induced myocarditis (CIM). Myocarditis can affect both the heart's electrical system as well as muscle cells causing abnormal ventricular depolarization and repolarization of the heart [1]. Left untreated, myocarditis can cause blood clots, strokes, heart attacks, and or heart failure. In general, treatment for myocarditis begins by identifying the underlying cause of the condition, which in some cases results from clozapine drug use [2].

Research shows that the use of clozapine correlates with cardiotoxicity more commonly than other antipsychotics [1]. Moreover, understanding the possible side effects of clozapine use and symptoms leading to myocarditis has not been fully explored throughout clinical studies. Most findings of CIM begin with heterogeneous symptomatology, similar to other, unrelated clinical conditions. The following case report (including a review of other CIM case studies) attempts to highlight identifiable factors involved in CIM, and what challenges are involved in overcoming certain issues related to its diagnosis.

The heterogeneous symptomatology of CIM makes an accurate and timely diagnosis of the condition difficult at best; this vague symptomatology helps explain the lack of precise data on confirmed cases and the prevalence of the condition. Moreover, with the estimated frequency of CIM at only 1% of the general population, cross-referencing the most common clinical features in adverse reactions to clozapine is limited [3].

Based on statistical findings of CIM, it is generally understood that there are no typical symptoms of CIM. Clinical presentations of this condition vary from no symptoms to mild symptoms (such as myalgia, dyspnea or fever) to fulminant cardiogenic shock and death. To better recognize CIM, this case report focuses on 1) enhancing the understanding of the atypical antipsychotic drug clozapine, 2) analyzing the guidelines for monitoring patients with symptoms of myocarditis after clozapine prescriptive use, 3) identifying early signs and symptoms of clozapine cardiotoxicity, and 4) identifying other clozapine complications.

Case Report

History of the presenting illness

The patient is a 25-year-old African-American male with no pertinent medical history, but a history of bipolar I disorder (BID). He was admitted to a state psychiatric facility (after being committed as a person being mentally ill) and received treatment for acute decompensation due to symptoms arising out of nonadherence with medication. The patient initially presented to the ER with a two-week history of erratic behavior and run-on pressured speech, hyperverbal, and echolalia. He was diagnosed with BID and mania, severe with psychotic features; schizoaffective disorder was ruled out. The patient had stopped his medications about two months prior to being hospitalized. While an inpatient, his negative behavior escalated. He became extremely agitated, began throwing things about, yelling and screaming, and continuously disrupting the occupants and staff of the mental health ward. Patients and staff began to be frightened. Besides a predilection to violent behavior, the patient became hypervigilant, disorganized, and delusional, believing his food and beverages were being poisoned. After several failed trials of antipsychotic medication (no improvement in the patient's behavior), his care team decided to initiate treatment with clozapine.

The patient was observed closely and monitored. By day two of clozapine treatment, the patient's troponin levels had peaked, EKG was remarkable for significant ST changes, labs were remarkable for leukocytosis, eosinophilia, and elevated CRP. The patient's physical condition deteriorated rapidly; he went into heart failure and required mechanical ventilation. The patient was then seen by a cardiologist who diagnosed the patient with drug-induced (clozapine) myocarditis.

Clozapine is a potent atypical antipsychotic medication used for the treatment of schizophrenia. It is typically considered a last resort medication when a patient has failed several trials of other antipsychotic medications. Clozapine is often associated with severe side effects that include inflammation of the heart muscles, relatively low white blood cell count, elevated blood glucose levels, postural hypotension, constipation, and dystonic reaction and other extrapyramidal symptoms (e.g., tardive dyskinesia). Also, antibiotics were initiated for suspected bacterial sinusitis. Other symptoms reported by the patient were as follows:

- Flu-like syndrome with body aches, chills, fatigue
- Dyspnea
- Cough
- Increased bladder tone
- Nausea/Vomiting/Diarrhea
- Palpitations
- Tachypnea

Lab results and vital signs

Table 1: *Lab Work I showing baseline lab results before initiation of clozapine.*

Note: *Initial set of lab work data obtained through blood test was used for control and comparison; unremarkable lab results.*

Test	Result
White Blood Count (WBC)	8.7
Absolute Neutrophil Count (ANC)	4.8
C- Reactive Protein (CRP)	0.71 (reference range 0.01 to 0.82)
Troponin 1	< 0.012

Table 2: *Lab Work II showing results after one week of clozapine usage.*

Note: *The second set of lab work data obtained through blood test was used to assess changes compared to baseline control; increase in CRP.*

Test	Result
White Blood Count (WBC)	7.5
Absolute Neutrophil Count (ANC)	4.4
C-Reactive Protein (CRP)	1.50
Troponin 1	< 0.012

Table 3: *Lab Work III obtained after the second week of clozapine usage.*

Note: *The third set of lab work data obtained through a blood test was used to assess changes compared to Lab Work II; increase in WBC, ANC, CRP, and troponin. At this juncture, the patient complained of flu-like symptoms, such as nausea, vomiting, and diarrhea; and became febrile with T-max of 100.6. Two days later, the patient reported a stiff neck; however, examination was unremarkable for radiculopathy or meningeal signs, but he remained febrile, T-max of 102.7. The patient was sent to the ER.*

Test	Result
White Blood Count (WBC)	11.3
Absolute Neutrophil Count (ANC)	9.5
C-Reactive Protein (CRP)	1.9
Troponin 1	0.016

Table 4: *Lab Work IV obtained after discontinuation of clozapine.*

Note: *The fourth set of lab work data obtained by a blood test was used to assess changes in the patient's condition compared to Lab Work III; decreased WBC, ANC, and abnormally high presence of bands and monocytes.*

Test	Result
White Blood Count (WBC)	6.0
Absolute Neutrophil Count (ANC)	3.4
BANDS	17%
Monocytes	15%

Table 5: *Vital signs I showing baseline vital signs before initiation of clozapine.*

Note: *An initial measurement of vital signs was used to assess basic bodily functions; unremarkable vital signs.*

Test	Result
Blood Pressure (BP)	117/67
Pulse Rate (PR)	86 BPM
Body Temperature (BT)	97.8 F
Respiration Rate (RR)	20 pm

Table 6: *Vital Signs II after one week of clozapine usage.*

Note: *The second measurement of vital signs was used to assess basic bodily functions. Abnormally high PR and BT was noted. At this juncture, the patient was diagnosed with a viral syndrome. Monospot was negative. Eosinophils were within a normal range. The patient was discharged back to the inpatient psych facility and continued with clozapine (100 mg Q HS). Two days later, the patient's condition worsened with the patient complaining of body aches, chills, and night sweats. The patient demonstrated greenish sputum draining into his throat from the sinuses, a slight cough, and chest discomfort. The patient was sent to the ER for further evaluation.*

Test	Result
Blood Pressure (BP)	121/79
Pulse Rate (PR)	110 BPM
Body Temperature (BT)	102.7 (02 sets: 94%)
Respiration Rate (RR)	16

Table 7: *Vital Signs III taken after the second week of clozapine usage.*

Note: *The third measurement of vital signs was used to assess basic bodily functions; abnormally high RR, BT, and RR.*

Test	Result
Blood Pressure (BP)	117/72
Pulse Rate (PR)	115 BPM
Body Temperature (BT)	102.4
Respiration Rate (RR)	34

Lab work summary

Baseline lab results (Lab Work I) appeared unremarkable. Lab Work II (lab results taken one week after initiation of clozapine) also appeared unremarkable, except for CRP +53% (however, still within tolerable limits). Lab Work III (obtained during the second week after initiation of clozapine) showed: WBC +33.7%; ANC +54%; CRP +21%; and troponin 1 +25% (compared to Lab Work II). These elevated factors in Lab Work III pointed to possible infection, drug reaction, presence of inflammation, trauma, presence of chronic disease to include heart disease and or myocardial infarction. Lab Work IV (obtained after the cessation of clozapine) showed: WBC -47%,; NC -64.3%;

bands measured at 17% which was on average 13% above normal levels, indicating that an injury and or inflammation had occurred; monocytes measured at 15% which was on average 5% above normal levels, also indicating that an injury occurred to include the possible presence of injured or dead cells.

Vital signs summary

Baseline vital signs (Vital Signs I) appeared to be unremarkable. Vital Signs II showed a slight increase in blood pressure (but still within normal range); resting heart rate (pulse rate) at 110 BPM (which is abnormally high, indicating tachycardia); body temperature of 102.7 F (indicating a fever); and unremarkable respiration rate. Vital Signs III revealed blood pressure within normal limits; resting heart rate (pulse rate) at 115 BPM indicating a continuation of tachycardia; body temperature of 102.4 F (indicating a continuation of a fever); and an abnormally high respiration rate of 34 RR (indicating non-specific presenting features).

Discussion

This patient was diagnosed with CIM. Pathologically, myocarditis is defined as an inflammatory disorder of the myocardium. Myocarditis symptomatology is heterogeneous or has inconsistent symptomatology, which makes it difficult to determine the incidence and explains the lack of data on specific incidence. The estimated occurrence of myocarditis induced by clozapine is about 1% and is rare, but the estimated occurrence for the general population to develop myocarditis is about 1.8 for every 10,000,000 people, which indicates CIM is 10,000 times higher in occurrence than myocarditis in the general population [3].

Standard doses of clozapine taken by this same population would seem to indicate that the effects are also non-dose-dependent. Clinical onset of symptoms occurs within two months of beginning pharmacological therapy. These nonspecific symptoms can be chest discomfort, arrhythmias, tachycardia, hypotension, dyspnea, fever, and myalgia. Cardiomyopathy and pericarditis may be observed during clozapine therapy. CIM refers to a contractile dysfunction of the myocardium and usually manifests with symptoms much later than those symptoms that occur with myocarditis [3]. Only a few cases of pericarditis has been reported in the literature, and is considered the rarest, but possible, manifestation from clozapine use [3].

Clozapine is an atypical antipsychotic or second-generation drug that is a tricyclic dibenzodiazepine. What distinguishes second-generation antipsychotics from first-generation antipsychotics is the increased efficacy of the drug for resolving symptoms and lowering the rate of extrapyramidal symptom that first-generation antipsychotics cause [4]. Clozapine is very effective for treatment-resistant schizophrenia or refractory schizophrenia in which positive symptoms are resistant to treatment. Introduced in 1961, clozapine has been life-changing for refractory schizophrenia, decreasing mortality rates via a significant decrease in suicide rates. However, the side-effect profile for clozapine has drawn criticism, initially due to resultant agranulocytosis, and more so and more recently due to the possibility of cardiac toxicity. Among affected patients who are biopsied, the peripheral eosinophilia and eosinophilic inclusions in the myocardium contribute to the current theory of the mechanism of CIM: that clozapine causes an immunoglobulin E-mediated hypersensitivity reaction [5]. However, these findings have not been consistent; therefore, other mechanisms for the cardiotoxicity are being considered.

Increased serum level of catecholamine in affected patients has been reported. This finding has prompted discourse on whether increased serum catecholamines are a result of or the cause of left ventricular (LV) dysfunction; there is evidence support the latter. The catecholamine, norepinephrine, was found in increased levels in the blood of affected patients. Other unproven mechanisms of CIM under consideration have to do with low serum selenium levels, calcium-dependent channel blockade, increased production of inflammatory cytokines, and cytochrome P450 enzyme deficiencies [3,5].

Although electrocardiograph findings and serum cardiac biomarkers (like creatine kinase troponin and C-reactive protein) are abnormal when muscle damage from myocarditis is significant, these presentations are nondiagnostic. Creatine kinase has proven to be subpar to troponin and of no value as a clinical indicator when screening for myocarditis due to its low predictive value. Troponin has been shown to be highly specific, but not consistently present in high numbers in affected patients [6].

The gold standard in diagnosing myocarditis is performing an endomyocardial biopsy. (The lack of that biopsy is a shortcoming in this report.) However, endomyocardial biopsies are not without inherent risks and limitations. Observer interpretation and insensitivity to the presence of focal myocarditis can reduce the likelihood of a definitive diagnosis. Performing endomyocardial biopsies as a blind invasive procedure creates risks and limitations. However; if imaging is used in conjuncture with endomyocardial biopsy to target lesions, the diagnostic yield may very well improve. It has been shown, using cardiac magnetic resonance imaging (cMRI), that the earliest lesion of inflammatory changes presents in the lateral wall of the left ventricle. This finding could be missed by nonimage guided biopsies.

The diagnostic imaging choice for myocarditis is cMRI; the characteristic finding is focal enhancement of the myocardium [7]. T2-weighted imaging can be used to diagnose myocarditis with high sensitivity and specificity. The use of gadolinium contrast can increase sensitivity from 84% to more than 90% [7,8]. Specificity holds at about 74% with cMRI. When using cMRI to diagnose myocarditis, two indicators of inflammation must be present as the standard. Also, cMRI can be used to distinguish between myocarditis and myocardial infarction; both conditions have similar presentations. The imaging can demonstrate differences between the midmyocardial wall being involved (myocarditis) and the subendocardial wall spared versus subendocardial wall affected early in myocardial infarction.

It is well documented that during congestive heart failure, there is an increased release of the hormone B-type natriuretic peptide (BNP) in response to increased wall pressure. This increased release of BNP is posited to be a reliable indicator of cardiac dysfunction in myocarditis, but there are few studies that validate this probable indicator. A small pilot study showed levels of elevated BNP in the serum while therapeutically treating with clozapine, yet BNP levels decreased significantly once treatment with clozapine ceased [9]. Evaluating BNP levels should help in monitoring asymptomatic myocarditis. The procedure to evaluate BNP is inexpensive, decreases the need for multiple echocardiograms, and promotes early detection.

With clozapine usage, once myocarditis, pericarditis, or cardiomyopathy has been detected and the condition diagnosed correctly, the primary treatment option going forward is the cessation of the drug. Patients should be treated in a supportive manner. With the cessation of clozapine, there can be functional recovery, resolution of cardiac dysfunction, and near complete reversal of LV dysfunction. After stopping clozapine, hemodynamics are addressed supportively as a priority by using positive inotropic agents. After such intervention, LV dysfunction may be addressed with beta blockers, angiotensin-converting enzyme inhibitors, or diuretics. In several studies, the use of corticosteroids in CIM was shown to be beneficial. Nevertheless, in other distinct studies, treating non-clozapine-related myocarditis with steroids did not result in significant improvement. The effects of such intervention in CIM were more effective in patients positive for eosinophilic inclusions. To date, there are few studies demonstrating any benefits of immunosuppressive therapy in patients with myocarditis.

Patients that only respond to clozapine treatment makes such treatment a perplexing ethical issue. Patients can be rechallenged with clozapine, but require close and repetitive monitoring to augment early detection of the reoccurrence of toxicity [10]. Returning a patient to the drug is not the treatment of choice, but if this is the last option, it is recommended that multiple echocardiograms are obtained periodically. Also, in such scenarios, the patient's consent is needed.

Drug Monitoring Recommendations

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Vital signs should be obtained every shift for the first week following initiation of this pharmacological treatment. Baseline lab work–which includes CBC with Diff, CRP, troponin, EKG, and echocardiogram–should be obtained before initiation, 7 days post-initiation, and at 14 days. Monitor the patient closely for signs and symptoms of heart failure within the first 2 weeks of treatment. Monitor the patient for hypotension and tachycardia, 3 times per day for the first 14 days. Combining the monitoring of symptoms and checking troponin, CRP, CBC and EKG results in enhanced identification of symptoms in myocarditis. Echocardiography should be performed at 6 months [5].

Conclusion

Clozapine can cause mild to severe to life-threatening adverse effects. There are, at times and under certain conditions, significant dangers with clozapine use. The clinician must remain vigilant to better safeguard patients taking clozapine who may be at risk for cardiotoxicity. Clozapine is used as a drug of last resort. Clozapine is a drug designed to improve behavioral conditions, such as bipolar I disorder and its subsequent symptoms. However, the side effects of clozapine may induce myocarditis, and subsequently lead to heart failure and or death. This case report focused on the benefits and hazards of the clinical use of clozapine, the potential effects, and any clinical presentations for the drug's usage. The percentage of CIM cases (wherein patients have used clozapine and showed homogenous side effects) is not well known. Thus, developing a "warning index" of signs and symptoms of CIM is challenging. Without a high level of awareness and or suspicion of the symptoms of CIM, the welfare of patients taking clozapine remains at risk.

There are too few clinical cases and reports concerning CIM to develop a prominent list of typical clinical findings indicating cardiotoxicity. Known symptoms of CIM tend to be heterogeneous and imitate conditions similar to viral infections, common colds, and bacterial infections, to name a few. Due to the shortfall of clinical cases available for the assessment of early symptomatology of CIM, patients (who must take clozapine) should be evaluated continuously; to include vital signs, baseline lab work, troponin, and EKG. Monitoring the patient's vital signs along with specific screening for cardiotoxicity, should be put and remain in place.

Further research into the effects of this psychotropic drug seems indicated and essential. In order to better understand CIM, more research is needed to provide additional data on the symptomatology of CIM and the warning signs for patients and clinicians. As further research on the adverse effects of clozapine usage is conducted, the awareness of the symptomatology of CIM will grow. Researchers should continually expand upon clinical findings so that the presentation of CIM is more fully understood and clinicians better understand how to monitor their clozapine patients, know what danger signals to look for in their patients, and know how to better treat patients who present with clozapine-induced myocarditis.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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